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CONTENTS Page

The Individuality of the American College of Physicians. REGINALD FITZ	1015
Homologous Serum Hepatitis. JAMES W. ROBINSON, DONALD N. TWADDELL and W. PAUL HAVENS, JR.	1019
Chronic Pulmonary Granulomatosis in Residents of a Community Near a Beryllium Plant: Three Autopsied Cases. CHARLES CHEESER	1028
Barbiturate Intoxication: A Clinical Electroencephalographic Study. ROBERT COHN, CHARLES SAVAGE and GEORGE N. RAINES	1049
Mumps Orchitis and Testicular Atrophy. I. Occurrence. CHARLES A. WERNER ..	1066
Mumps Orchitis and Testicular Atrophy. II. A Factor in Male Sterility. CHARLES A. WERNER	1075
The Mechanics of Deformities of the Hands in Atrophic Arthritis, and a Discussion of Their Prevention and Correction. JAMES C. SMALL	1087
The Technic and Diagnostic Value of Aspiration of Bone Marrow from the Iliac Crest. MICHAEL A. RUBINSTEIN	1095
The Treatment of Bacterial Endocarditis. EDWARD S. ORGAIN and CHARLES K. DONEGAN	1099
Polyarteritis Nodosa: A Clinical and Pathological Study and Report of Six Cases. MORTON H. ROSE, DAVID LITTMANN and JOHN HOUGHTON	1114
Massive Hemorrhage from Peptic Ulcer: Prognosis and Treatment; Conclusions Drawn from a Large Series Treated in a Municipal Hospital. H. B. CATES ..	1144
Torulosis of the Central Nervous System: Review of Literature and Report of Five Cases. WILLIAM H. MOSBERG, JR. and JAMES G. ARNOLD, JR.	1153
Case Reports:	
Achalasia (Cardiospasm); Report of a Case with Extreme and Unusual Manifestations. C. T. BELLO, J. R. LEWIN, C. M. NORRIS and G. E. FARBER, JR.	1184
Mercurial Diuretics: Some Hazards of Mercurhydrin; Report of Two Cases with One Death. ALFRED WALLNER and LAWRENCE HERMAN	1190
Monocytic Leukemia, an Uncommon Cause of Renal Failure. R. D. TAYLOR, ROBERT BIRCHALL and IRVING H. PAGE	1197
Splanchnicectomy for Hypertension in Lupus Erythematosus and Periarthritis Nodosa. S. F. HORNE, A. C. CURTIS and E. A. KAHN	1202
Metastatic Adenocarcinoma of the Thyroid with Elevated Basal Metabolism; Radiologic Studies. S. J. WEINBERG, R. M. FINK, KAY FINK and G. L. PACKER	1207
Fatal Aplastic Anemia Occurring during Anticonvulsant Therapy: Probable Idiosyncrasy to Phenurone. THOMAS W. SIMPSON, EDWIN B. WILSON, JR., and S. L. ZIMMERMAN	1224
Editorial—Uses and Hazards of the Organic Phosphate Anticholinesterase Compounds	1229
Reviews	1235
College News Notes	1240
Index	1261

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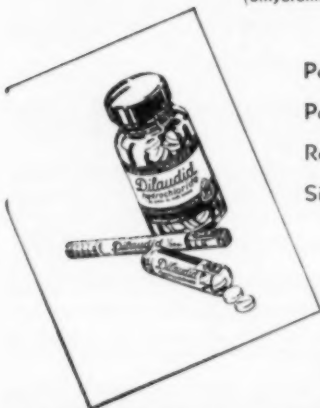
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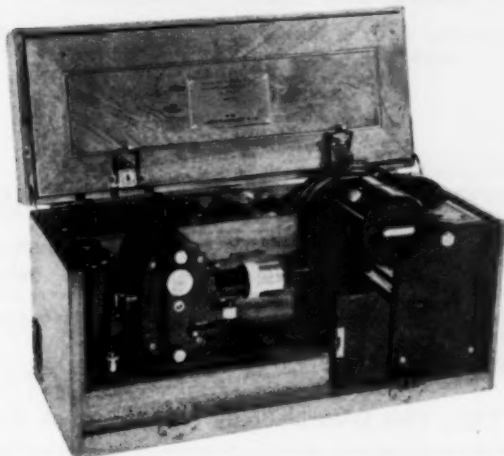
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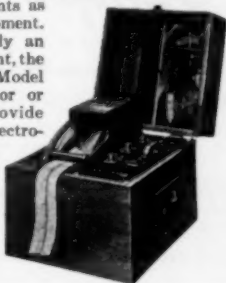


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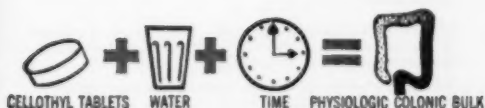
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1. *Gastroenterology* 13:275 (Oct.) 1949. 2. *N. Y. State J. Med.* 48:1822 (Aug.) 1948.



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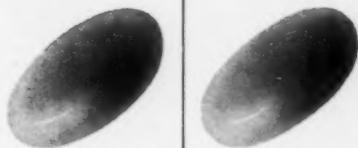
1. Friedlaender & Friedlaender: Amer. Pract. 2:643, June, 1948

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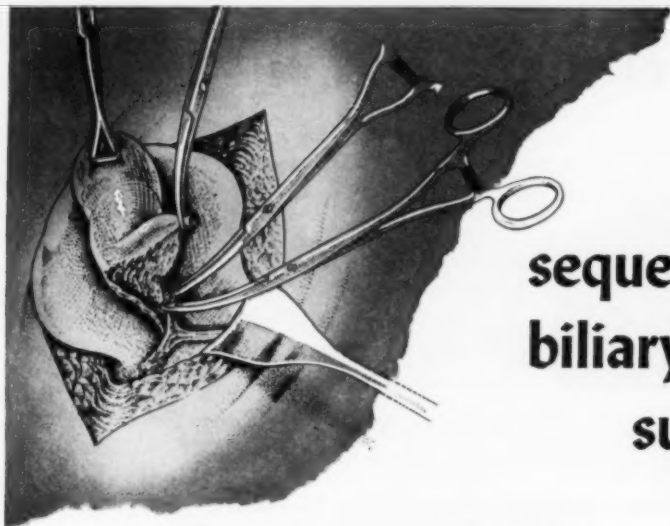
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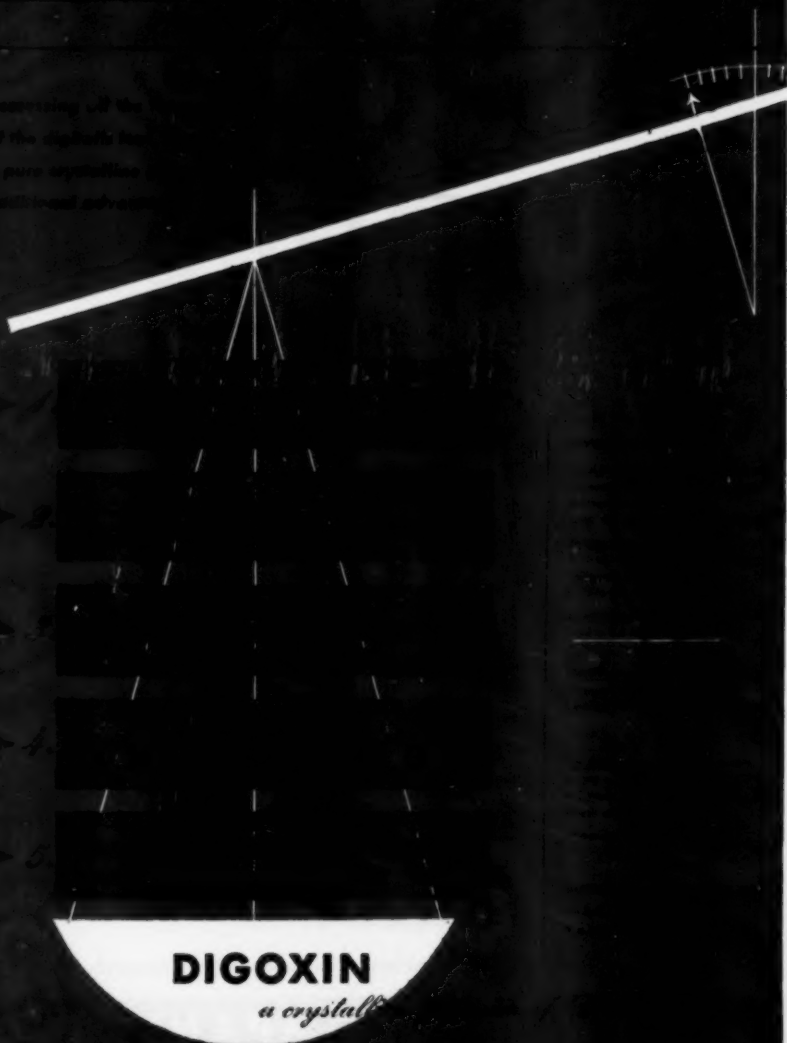
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2. Bell, George O., Bradley, Robert B., and Hurxthal, Lewis M. Paroxysmal Tachycardia: Experiences with Massive Doses of Quinidine Intravenously in an Refractory case. *Circulation* 1 — 939 - 969 (April, Part II) 1950.

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Bibliography: 1. Lovelace, M. H., and Duran, M.: J. Am. M. Women's A. 4:105, 1949. 2. Schiller, I. W., and Lowell, F. C.: New England J. Med. 240:215, 1949.

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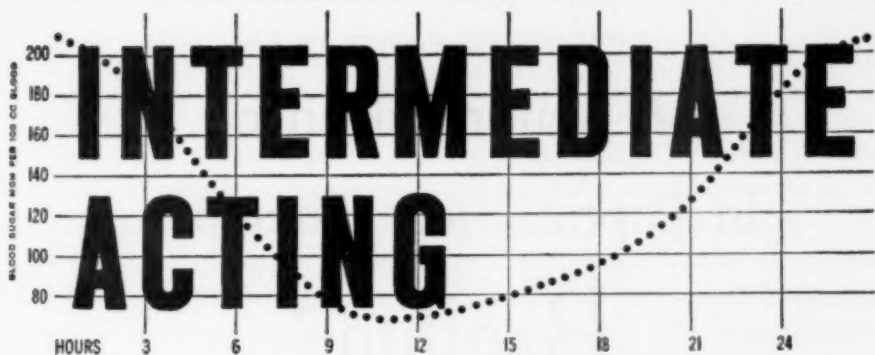
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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. *ibid* Proc. Am. Diabetes Assn. 8:37, 1948.



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A Major Advance in Peptic Ulcer Therapy

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It is important that the usual high night secretions be controlled. To this end it is recommended that the night

dose be taken six hours prior to the usual time of arising. Further, after the ulcer is healed, it is important that the patient be placed on a maintenance dosage schedule if he is to have a reasonable assurance of nonrecurrence. The maintenance dosage may well be approximately one-half the therapeutic dose and no evidence of chronic toxicity has been observed in maintenance dosage although this experience covers only a period of sixteen months.

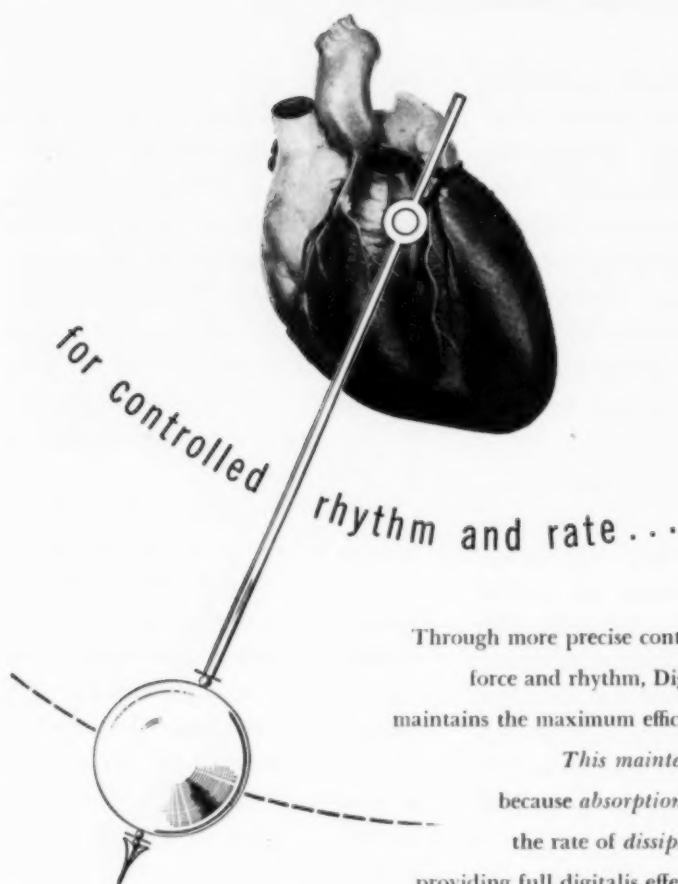
Patients may report dryness of the mouth, mild degrees of blurring of vision, slight difficulty of urination or gastric fullness; these symptoms usually decrease or disappear on continued medication but if they are severe they may require dosage adjustment. Untoward reactions with Banthine therapy have not been encountered.

More complete suggestions for Banthine administration are available to the medical profession in Searle Reference Manual No. 40.

Banthine is a product of Searle research. G. D. Searle & Co., Chicago 80, Illinois.

REFERENCES

1. Longino, F. H.; Grimson, K. S.; Chittum, J. R., and Metcalf, B. H.: An Orally Effective Quaternary Amine, Banthine, Capable of Reducing Gastric Motility and Secretions, *Gastroenterology* 14:301 (Feb.) 1950.
2. Grimson, K. S., and Lyons, C. K.: Scientific Exhibit at the American Academy of General Practice, St. Louis, Feb. 20-23, 1950.
3. Grollman, A.: *Pharmacology and Therapeutics*, ed. 14, Philadelphia, Lea & Febiger, in press.
4. Dragstedt, L. R.: Personal communication, March 23, 1950.
5. Collins, E. N.: Personal communication, March 28, 1950.



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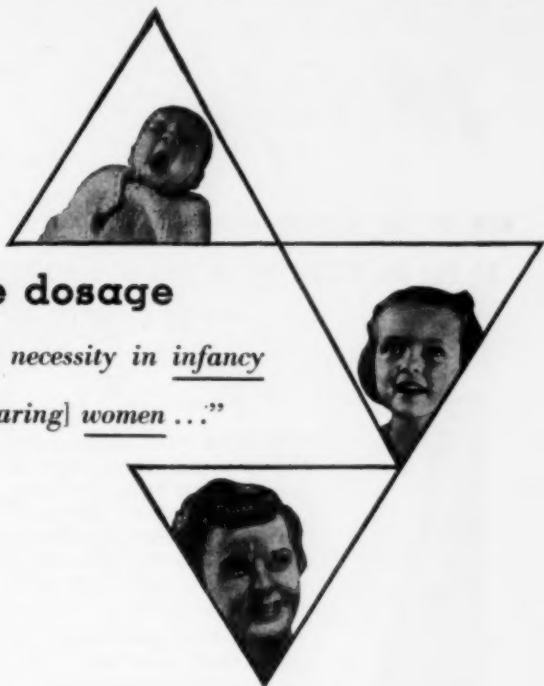
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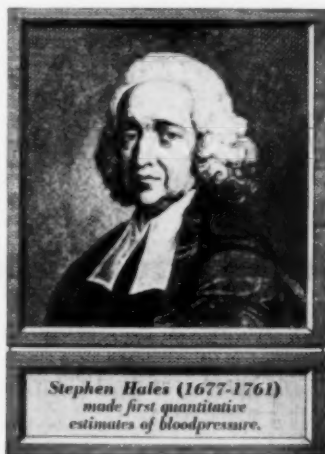
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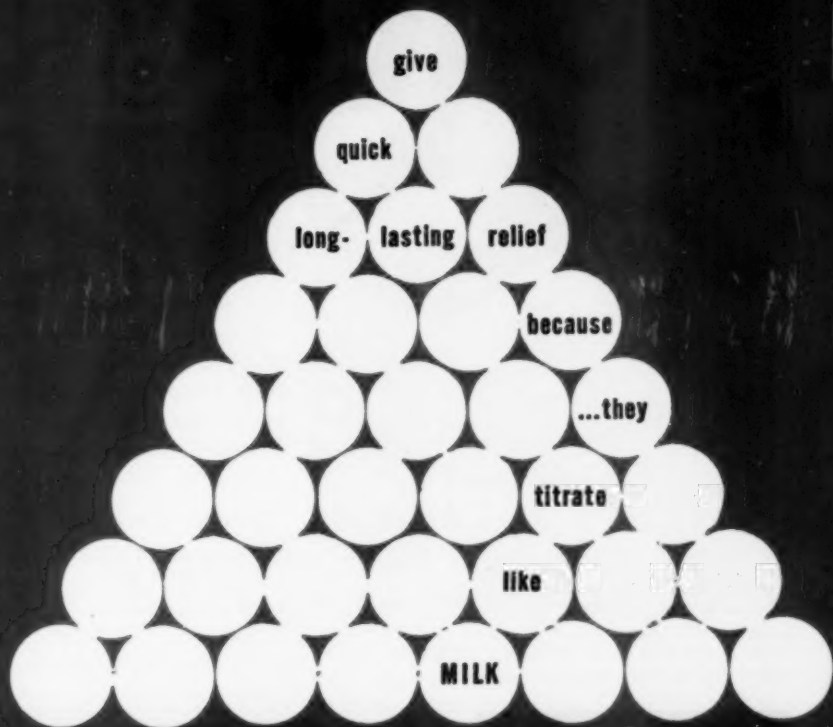
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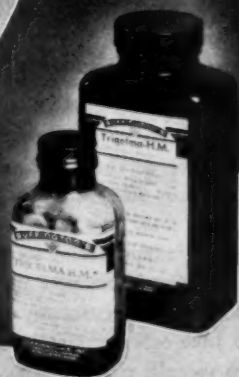
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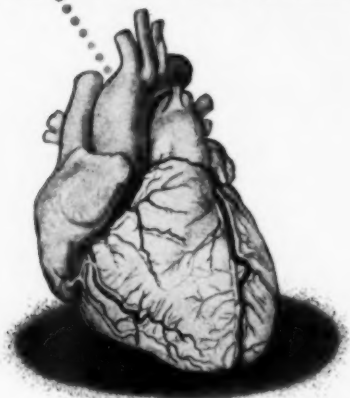
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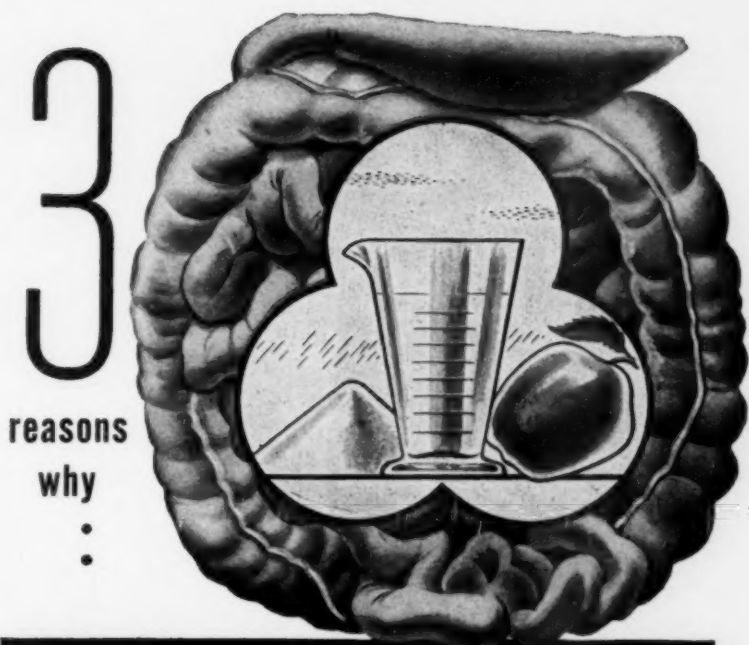
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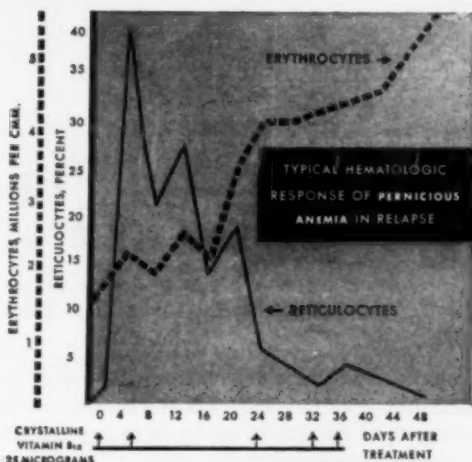
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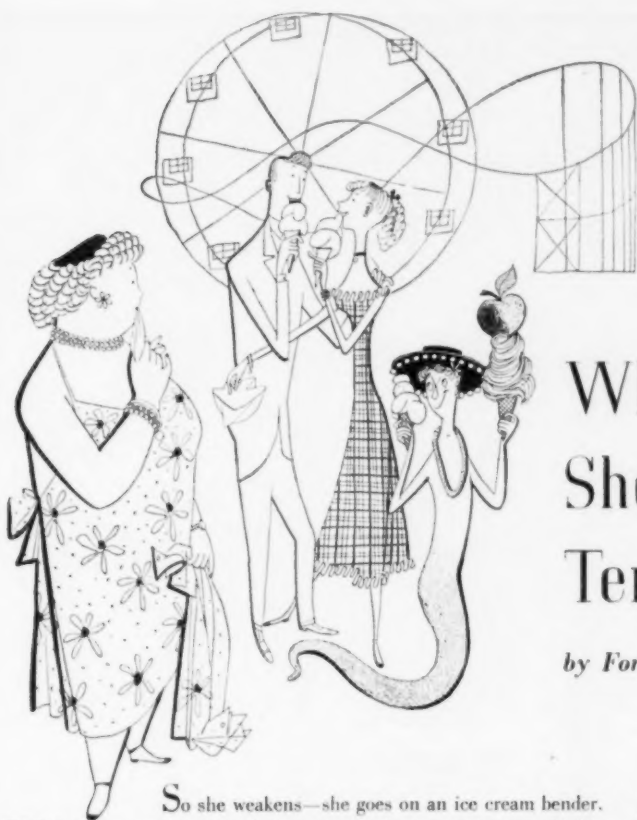
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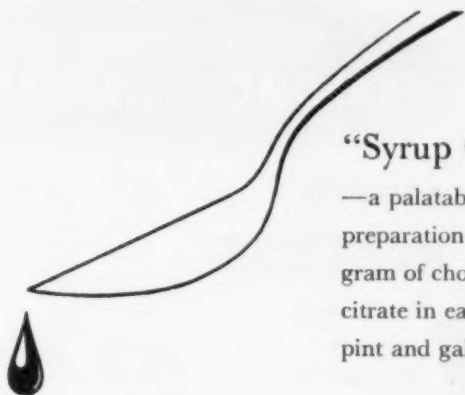
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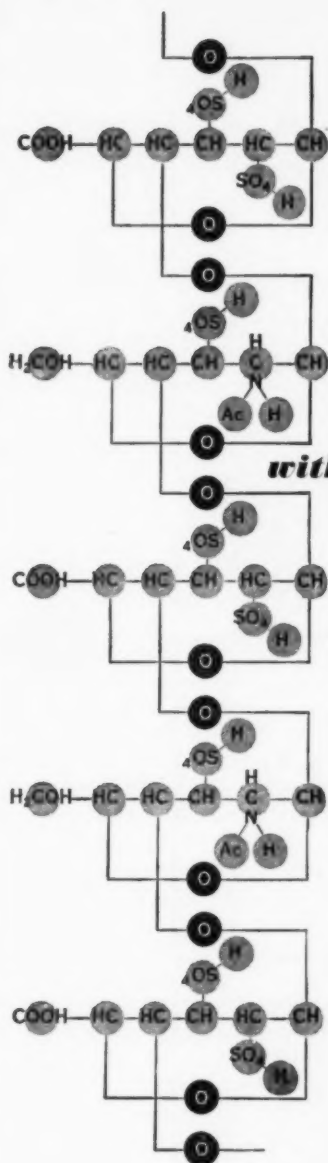
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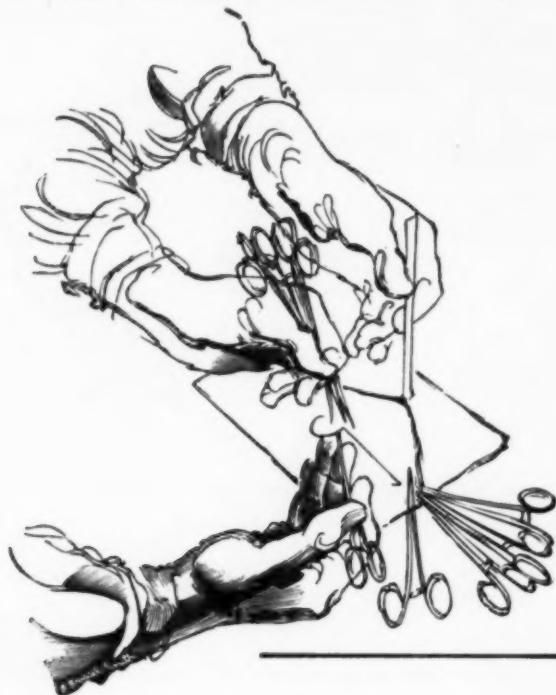
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ANNALS OF INTERNAL MEDICINE

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THE INDIVIDUALITY OF THE AMERICAN COLLEGE OF PHYSICIANS*

By REGINALD FITZ, F.A.C.P., *Boston, Massachusetts*

THE by-laws of the College stipulate that the President shall deliver an address at each annual Convocation. In fulfilling this obligation my predecessors in office have chosen for consideration a wide range of subjects; in early days, and chiefly for the benefit of new Fellows, the President often limited his remarks to a review of the immediate affairs of the College. This is a precedent which I propose to revive on this occasion.

Many years ago Dr. Harvey Cushing read a delightful paper at an Ether Day celebration in the Massachusetts General Hospital. He began by saying that as human beings were pretty much alike inside so were institutions; they differed chiefly—both institutions and individuals—in their appearance, in their occupation, and in their personality. After this introduction he described the Massachusetts General Hospital as though it were alive and human—which indeed it is—and he showed how much its present vigor depended on certain traditions which had combined over the years to give it unique individuality.

The American College of Physicians, like the Massachusetts General Hospital, is a lively and human institution. To be sure, it is young as colleges go, but it has been carefully brought up because since it was born it has been nourished on nothing more substantial than ideals: the Founders hoped that the College would always promote the science of medicine, that it would further the study of medicine, that it would recognize distinguished medical achievement, and that it would encourage a spirit of friendliness among its members. These aims have been kept in mind constantly—and always will be, I hope—by each succeeding generation of Officers, Regents, Governors, and Fellows.

As to any other creature which is growing fast, so to the College is any new undertaking an exciting adventure; a baby first creeps, then walks, and finally learns to leap forward. The College, I believe, has passed the creep-

* President's address, Thirty-First Annual Session, American College of Physicians, Boston, Mass., April 19, 1950.

ing stage and now is walking with considerable confidence; at least it has already taken four long steps forward.

Sixteen years ago, at the suggestion of a committee headed by Dr. David Barr of New York, our Research Fellowship program was initiated. Our Research Fellows, almost without exception, have proved productive contributors to medical knowledge and several have come to occupy important teaching or research positions in medical schools. The impetus which these men obtained through the College at the beginning of their careers has seemed an important influence in helping them later to achieve national prominence. Certainly, to afford carefully selected young doctors ample opportunity to engage in research in suitable environment is a rational way to promote the science of medicine. So far, the experiment along this line has yielded impressive results. As a new project, along a closely parallel line, the College in conjunction with the Kellogg Foundation has recently assumed responsibility for directing the postgraduate educational course in this country of certain young Latin-American physicians. This development is still so new as to warrant no special comment; it shows, however, how eagerly the College wishes to encourage a better understanding of medicine wherever possible.

The College already has promoted the science of medicine and furthered its study in other important ways. The *ANNALS OF INTERNAL MEDICINE*—our own medical journal—first appeared in 1920. During the ensuing thirty years it has been directed by only three editors, each managing to add something of himself to increase the periodical's usefulness and popularity. At present it has more than 14,000 subscribers so that it is now one of the most widely circulated medical journals in existence. Each issue is always well turned out; the original articles, the case reports, the editorials, and the book reviews are carefully prepared, well written, and well illustrated. This record speaks for itself.

Fifteen years ago, Dr. Ernest Bradley of Lexington, Kentucky developed a plan by which, from time to time, regional meetings of the College sponsored by various Governors came to be held within their own territories. He anticipated that such meetings might prove stimulating not only to Fellows in the neighborhood but also to Associates and to many other physicians both young and old. This scheme, also, has proved successful. During the past year, for example, there have been seventeen regional meetings, each one attracting a large and enthusiastic audience. Their success has wholly depended on the ingenuity of their sponsoring Governors, and to develop a full day's program of advanced medicine, a program emphasizing newly acquired knowledge, and a program delivered by competent experts, is no mean achievement. Yet our Governors now manage to do this in many different parts of the country regularly, adding, thereby, invaluable encouragement to advanced medical study under College leadership.

The more strictly academic work of the College has consisted in our annual sessions and in postgraduate courses which include various phases of internal medicine.

For many years the program of the Annual Session has followed a standard pattern: for five days those who attend are kept as busy as they wish with morning clinics, noon-day round table discussions, and afternoons of short presentations by distinguished speakers drawn from all over the world. The construction of the program is more or less like the preparation of a book which appears in a new edition each year; an accurate record is kept of topics which seem of greatest general interest and of complaints which are received. As soon as one meeting is over, plans are begun for the next, each new Editor-in-Chief attempting to develop a session which will prove interesting, of educational value to all in attendance—and one which will provoke no more than a normal amount of derogation.

The idea of the College's offering short postgraduate courses came to life thirteen years ago when Dr. Herman Mosenthal of New York proposed it. Now, a diversified curriculum covering many fields of internal medicine is given in several different medical centers by faculties nominated by the College. The faculties are carefully chosen, the subject matter of each course is scrutinized critically, and the result is that a thousand or more Fellows benefit each year from an unusual form of intensive postgraduate education pitched at the highest possible level. Anyone who has taken one of the courses has been pleased with the result; he works hard at his studies for a week or ten days but returns to his normal labors invigorated and refreshed.

Under such nursing, the College has become astonishingly popular. Dr. Charles F. Martin of Montreal once commented on its growth by saying how remarkable it was that an institution of learning which offers no diploma and no reward more tangible than the right to sign the initials F.A.C.P. after one's name could quickly rise from very humble origin to become one of the most powerful medical organizations in the country. The basic reason, I believe, depends in part on the way in which the College promotes the science and study of medicine and, in part, on the manner in which it recognizes distinguished medical achievement, but also, and to a large extent, on its underlying spirit.

Presently, Fellows to be inducted will be asked to subscribe to the Fellowship Pledge. This particular ceremony has been observed at every annual session; besides having an element of picturesqueness, it serves as a method of indoctrination to new members—some of whom will later be Officers, Regents or Governors. It can never do harm to remind them, through the dignified recital of certain Hippocratic aphorisms, that Medicine to the American College of Physicians is a profession, not a trade, and that to make it continue so it must be governed by standards rather than by laws.

The College salutes medical achievement in its own fashion; the way it does so at the Convocation, through various awards, is of enough historic interest to be worth mentioning.

To be made a Master of the College is a significant compliment; there are at present only twelve living Fellows who have the right to call themselves Masters of the American College of Physicians—each being chosen for the

honor primarily because he was, in fact, a Master Physician, and in the second place, because the College knew him as a warm and loyal friend.

On the rolls of the College are three names which have been perpetuated less impersonally.

Dr. James Deacon Bruce, who was elected President in 1940, was particularly interested in postgraduate education and public health. He felt that in future Preventive Medicine would, by necessity, play an increasingly important part in medical practice; hence, each year, in his honor, and by his generosity, we have the Bruce Memorial Lecture delivered by a pre-eminent authority in the field of medicine which so greatly interested him.

Dr. John Phillips was a Regent at the time of his death in the Cleveland Clinic disaster of May 15, 1929. He played an important part in raising College standards, always looking forward and thinking in terms of progress to be made by research. Each year, in his honor, we have the John Phillips Memorial Lecture delivered by a distinguished investigator whose work has opened new pathways for the better care of sick people.

Dr. Alfred Stengel was our fourth President, an accomplished internist, a distinguished medical scholar and teacher, and a Fellow profoundly influential in laying solid foundations for the College on which to build, in days to come, an enduring superstructure. He was a close friend of Dr. Bruce's who hoped that the College would never forget him; thus, the Alfred Stengel Memorial Award is given periodically to that Fellow who seems best to have captured Dr. Stengel's viewpoint and spirit, while the Alfred Stengel Research Fellow designates that Research Fellow appointed in any year who seems to offer greatest promise of proving a worthy disciple of so fine a leader.

These memorials are significant and I hope that others like them will come into being as time goes on. A College needs traditions with which to color its personality and must always bear in mind, as it goes forward, how much it owes to notable figures of its past.

The College today represents a great deal more to American medicine than merely a large and popular medical society. I have attempted to describe something of its individuality, hoping that each new Fellow will find it attractive and will feel a strong sense of pride in becoming part of it; it can maintain its present reputation only if every Fellow contributes to its progress.

As Dr. Cushing said, people who are willing to do something more than follow a prescribed routine and who merge themselves intimately with the active, indoor life of an institution, giving, even at personal sacrifice, the most time to the attainment of the end, are certain to be the best and longest remembered. In the case of the College, unselfish devotion and loyalty have already endowed it in youth with force and vigor; as time marches on, unselfish devotion and loyalty will prevent its growing old and will keep its youthful spirit renewed.

HOMOLOGOUS SERUM HEPATITIS *

By JAMES W. ROBINSON, M.D., *Summit, N. J.*, DONALD N. TWADDELL,
M.D., *Dundee, N. Y.*, and W. PAUL HAVENS, JR., M.D.,
Philadelphia, Pa.

HOMOLOGOUS serum hepatitis has been classified as a viral disease, transmitted by the parenteral inoculation of human blood or its products obtained from carriers of the causative virus. The exact relationship of this *artificially transmitted* disease to the *naturally occurring* infectious hepatitis is not known, and the question has been raised as to whether homologous serum hepatitis is not merely the result of the artificial transmission of a virus which, under natural conditions, causes sporadic or epidemic infectious hepatitis.¹ This is probably true more often than is suspected, although there is no evidence to indicate that it is always the case. Actually, certain epidemiologic and experimental data suggest that, at least in some instances, different viruses or possibly different strains of the same virus are operative in causing the two forms of disease.^{2, 3}

Homologous serum hepatitis may be transmitted by the use of contaminated syringes or needles,⁴⁻⁷ or by the administration of convalescent human serum,^{8, 9} vaccines containing human serum,^{10, 11} or transfusions of plasma or blood containing hepatitis virus.^{12, 13} In the past few years, hundreds of thousands of cases of such artificially transmitted disease have occurred among military personnel and civilians in different parts of the world. Recent reports¹⁴⁻¹⁷ have called attention to the occurrence of this form of hepatitis following transfusions of pooled plasma in civilian hospitals. The incidence of disease and its greater severity in older and debilitated patients in both civilian and military groups have curtailed the use of pooled plasma in many hospitals and limited the number of donors contributing to pools in other institutions.

The importance of homologous serum hepatitis warrants the recording of all pertinent data, and it is the purpose of this paper to describe the experience with this disease at the Pennsylvania Hospital from August 1942 to August 1947.

MATERIALS AND METHODS

During this five year period, the blood bank of the hospital was operated in the following manner: Brief histories were obtained from donors in order to exclude those with recognizable transmissible disease. In the earlier years, inquiry regarding jaundice was not specifically made. Observations

* Received for publication April 28, 1949.

From The Pennsylvania Hospital and The Jefferson Medical College, Philadelphia.

This investigation was conducted, in part, with the aid of the Commission on Virus and Rickettsial Diseases, Armed Forces Epidemiological Board, Office of The Surgeon General, U. S. Army, Washington, D. C.

were made of the body temperature, blood pressure, and skin, as well as determinations of the level of hemoglobin and Eagle precipitin reaction of the blood. The blood from each donor was collected aseptically in amounts of 500 c.c. into individual bottles containing 5 per cent sodium citrate. In the last year of the period of study, the anticoagulant used was a solution containing 2.13 per cent sodium citrate, 0.67 per cent citric acid, and 2 per cent dextrose. The citrated blood was stored in refrigerators at 37° to 40° F. until used. At the end of five days—or, in later years, following the introduction of the compound anticoagulant, at the end of 21 days—the plasma was removed from the blood, and pools were made incorporating plasma from several donors. The number of donors in these pools varied from 9 to 22, averaging 16. From such pools, units containing 250 c.c. of plasma each were prepared, frozen, and stored at -4° C. until used.

The incidence of homologous serum hepatitis in the Pennsylvania Hospital was determined by a review of the records of all patients diagnosed during the period of five years according to the following nomenclature: (a) acute catarrhal jaundice; (b) infectious hepatitis; (c) homologous serum hepatitis; or (d) other unlisted diseases of liver and biliary tract. Patients were selected in whom jaundice appeared several weeks following the administration of blood and/or plasma. Of these, a considerable number showing other possible causes of jaundice was excluded. The remainder of the patients who are discussed here meet the criteria now available for the diagnosis of homologous serum hepatitis. These criteria include the characteristic clinical course of acute hepatitis occurring in patients who received plasma and/or blood at an appropriate interval (28 to 145 days) before the onset of hepatitis. Deflection from normal of certain tests of hepatic function, including bromsulfalein dye retention, cephalin-cholesterol flocculation, and thymol turbidity tests, added confirmatory evidence. All patients included in this report had clinical jaundice. Necropsy was performed on one patient, and necrosis of the hepatic parenchyma consistent with the diagnosis of viral hepatitis was found.

RESULTS

During the five year period from 1942 to 1947, 15 cases of hepatitis presumably due to transfusions of plasma and/or blood occurred. Of these, three received the probably icterogenic material in other hospitals; the remaining 12 received blood and/or plasma at the Pennsylvania Hospital. During this time, there were in the hospital 454 beds, with an annual admission rate (1946) of 9,896, and an average daily census of 322 patients. Of the 15 cases presented, none occurred in 1942, one in 1943, three in 1944, two in 1945, four in 1946, and five in the first seven months of 1947.

The 15 patients ranged from 21 to 70 years in age, with an average of 52 years. When considered by decades, this represents an incidence of three in the third decade, two in the fourth, three in the sixth, and seven in the

seventh. The group included 10 males and five females. Thirteen patients were white and two were colored, the latter both females.

The majority of patients (11) received blood and/or plasma in relation to surgical procedures. Four medical patients were included in the group. The incubation period for each patient was calculated from the date of administration of plasma and/or blood to the recognition of jaundice. When more than one transfusion was given, minimum and maximum incubation periods were determined for both blood and plasma. For blood, the minimum and maximum possible incubation periods ranged from 28 to 117 days. For plasma, the minimum and maximum possible incubation periods ranged from 28 to 145 days.

In certain cases, the exact date of appearance of jaundice was not known and, in addition, certain patients were discharged from the hospital with slight icterus, so that the exact date of disappearance of jaundice was not determined. However, the figures available indicate that the duration of jaundice ranged from a minimum of 11 days to at least 80 days, with a roughly estimated average of 25 days. In some instances, jaundice was not the first symptom but was noted seven to 10 days following nausea, epigastric discomfort, or low-grade fever. In most cases, the course was benign and improvement rapid, but death occurred in three patients, giving a mortality rate of 20 per cent for this small group. The duration of jaundice in those who died was, in general, shorter (11, 13 and 28 days, respectively), and the course more fulminant. In table 1 are recorded certain pertinent data about the course of disease in the 15 patients.

Source of Icteric Material. Of the 15 cases, eight received plasma alone, six both plasma and blood, and one received blood alone. Thus, pooled plasma, the more likely carrier of hepatitis virus, was received by 14 (93 per cent) of the patients. This is in agreement with the reports of others who have found the incidence of hepatitis following transfusions of pooled plasma many times greater than following transfusions of blood. The statistical importance of multiple donors to pools of plasma in increasing the chance of contaminating any given pool has been emphasized.

Attempts were made to investigate each pool of plasma and/or transfusion of blood received by the 15 patients who developed acute hepatitis. Efforts were made to determine the presence of hepatitis among the donors to the incriminated pools, as well as the incidence of hepatitis among other recipients of the same pools, but follow-up studies were disappointing. A large number of the donors were seamen, military personnel, or transient residents of the community during the war years, rendering contact with them virtually impossible. One donor had a history of jaundice in 1936, nine years before he contributed plasma to Pool No. 29 which was subsequently presumed to be icterogenic. The exact significance of this is undetermined although the possibility of a carrier state existing long after recovery from hepatitis must be considered. The investigation of the other recipients of plasma presumed to be icterogenic was also incomplete. A certain number of the recipients had died, and contact with many of the

TABLE I

Probable Source of Hepatitis Virus, and Duration of Incubation Period and Jaundice in 15 Patients with Homologous Serum Hepatitis

Case	Sex	Age	Primary Disease	Transfusions			Duration		Maximum Measured Serum Bilirubin	Result
				Blood	Plasma		Intervals between Transfusion and Jaundice	Jaundice		
				c.c. 5 10	c.c. 150 150	Pool No. 81 89	days 57-117	days 20	mg. % 4.3	
1	F	25	Spontaneous pneumothorax*							Recovery
2	M	66	Hyperthyroidism Thyroidectomy		250	29	61	21	9.6	Recovery
3	F	65	Sarcoma of uterus Hysterectomy Radium therapy	500	250	29	28-32	30+	27.5	Recovery
4	M	62	Myocardial infarction Epidermoid carcinoma of penis		1750	32, 33, 35	47-50	30	26.0	Recovery
5	M	68	Benign hypertrophy of prostate Prostatectomy		250 250	63 64	39-41	50	27.3	Recovery
6	M	65	Benign hypertrophy of prostate Prostatectomy		200 200	72 73	100-110	80	24.4	Recovery
7	M	38	Malignant hypertension Sympathectomy		500	?	143-145	28	12.0	Death
8	M	67	Ureteral calculus Pyloric ulcer with perforation	1000			86-92	13	10.5	Death**
9	M	57	Rectal polyp Resection	?	?	?	45-77	11	13.3	Death
10	F	54	Fractured ribs; lacerated scalp		500	?	141	12+	7.4	Recovery
11	M	40	Acute glomerulonephritis	2000	1000	?	74-88	39+	20.0	Recovery
12	M	58	Adenocarcinoma of colon Resection	1500	1500	4, 5, 6, 7	97-105	30	27.2	Recovery
13	F	21	Retained placenta	?	?	?	30	30+	33.5	Recovery
14	F	29	Lacerated scalp		250	?	77	7+	21.5	Recovery
15	M	70	Varicose veins Subfacial dissection		250	99	65	31	9.0	Recovery

* Blood and plasma given intrapleurally.

** Necropsy revealed acute necrosis of the liver.

? Indicates unknown amount of blood or plasma, or number of pool of plasma.

+ Indicates exact duration of jaundice not known.

others was impossible. However, hepatitis occurred in at least two recipients (Cases 2 and 3) of one pool of plasma (No. 29), strongly suggesting that it was icterogenic.

Incidence of Ictericogenic Pools of Plasma Made at the Pennsylvania Hospital. Before 1946, the data concerned with donors and recipients were not complete. However, in the 19 month period from January 1946 to August 9, 1947, it was possible to determine in some degree the incidence of hepatitis with jaundice following transfusions of plasma and/or whole blood given at the Pennsylvania Hospital. During this period, 64 pools of plasma were made from the blood of 1,143 donors, with a range of 9 to 22

donors per pool. This plasma was given to 621 recipients of whom six developed acute hepatitis after an appropriate incubation period. Two of these patients (Cases 1 and 3) also received whole blood. The possibility that these two patients were infected by blood rather than plasma must be considered, but the likelihood of this is not great in view of the known greater infectivity of plasma. In further support of this is the fact that the plasma received by one of them (Case 3) was from Pool No. 29 which produced hepatitis in another patient (Case 2). During this same period, 1,635 patients received one or more transfusions of citrated blood from 4,294 donors. Only one patient who received blood alone developed homologous serum hepatitis. Although the incidence of disease is apparently low (0.96 per cent after pooled plasma, and 0.06 per cent after blood), the incompleteness of follow-up, in addition to the difficulty in the diagnosis of sub-icteric hepatitis, makes possible the concept that the actual incidence of disease may have been greater.

Of particular importance, however, is the fact that, although the incidence of hepatitis was apparently low, the percentage of potentially icterogenic pools of plasma was high. The six patients who developed hepatitis had received 10 different pools of plasma. Two patients (Cases 2 and 3) received the same pool (No. 29), emphasizing its probable icterogenic capacity; three patients (Cases 1, 5 and 6) received two different pools each; and one patient (Case 4) received three pools. Thus, if all pools were contaminated, the incidence of infected pools of plasma during this period would have been 10 out of 64, or 16 per cent. If only a single pool given to each recipient was contaminated, the incidence would be five out of 64, or 8 per cent. Below are summarized the case histories of these six patients.

Case 1. A 25-year-old white female was first admitted to the Pennsylvania Hospital in August 1946 with spontaneous pneumothorax of undetermined cause. During the succeeding months, there were several recurrences of bilateral pneumothorax, requiring frequent decompression. On March 21, 1947, an attempt was made to produce pleural adhesions by the injection of 150 c.c. of pooled plasma (Pool No. 81), 5 c.c. of fresh citrated blood, and 150,000 units of penicillin into the left pleural cavity. The blood was taken from a member of the hospital staff who had no history of preceding jaundice. Again on May 20, 1947, 150 c.c. of pooled plasma (Pool No. 89), 10 c.c. of fresh citrated blood (taken from the patient), and 200,000 units of penicillin were injected into the right pleural cavity. On July 9, 1947, she had anorexia, nausea and dark urine, and on July 16 (57 and 117 days after previous instillations of blood and plasma), she noted icterus of the sclerae. Physical examination on July 19 revealed bilateral pneumothorax. Jaundice of the skin was present but the liver was not palpable or tender. Laboratory data: The leukocytes numbered 6,700/cu. ml. The serum bilirubin measured 4.3 mg. per cent, declining in 15 days to 1.02 mg. per cent when the bromsulfalein dye retention test revealed 15 per cent of dye retained in 30 minutes. She improved rapidly, and was discharged August 8, 1947, when jaundice was no longer discernible.

Case 2. A 66-year-old white man had a subtotal thyroidectomy for hyperthyroidism performed March 1, 1946, at the Pennsylvania Hospital. Post-operatively, he received 250 c.c. of pooled plasma (Pool No. 29), and was discharged from the hospital after an uneventful recovery. He was re-admitted May 8, 1946, with a his-

tory of jaundice of one week's duration, first observed 61 days following the single transfusion of plasma. He had no other complaints. Physical examination revealed jaundice of the skin and sclerae; the liver was not palpable or tender. Laboratory data: The leukocytes numbered 9,000/cu. ml. The serum bilirubin measured 9.6 mg. per cent. The urine contained bilirubin, and urobilinogen in a dilution of 1:80. Nineteen days later, the serum bilirubin measured 1.0 mg. per cent. He was discharged without discernible icterus on June 3, 1946.

Case 3. A 65-year-old white housewife with hypertensive cardiovascular disease was admitted to the Pennsylvania Hospital on February 20, 1946, for the removal of leiomyomas of the uterus. On February 23, she received 500 c.c. of citrated blood; and post-operatively, on February 25, she was given 250 c.c. of pooled plasma (Pool No. 29). Sarcomatous changes were found in the uterine leiomyoma and, on March 20, radium was inserted in the vaginal vault for a total of 4,000 milligram hours. On March 22, she developed anorexia, diarrhea and elevation of temperature to 100° F. On March 24 (30 days after receiving the blood, and 28 days after receiving plasma), jaundice was first noted. Physical examination at that time revealed icterus of the skin and enlargement and tenderness of the liver, with the lower border palpable 8 cm. below the costal border on the right. The spleen was palpable 5 cm. below the costal margin, and was firm and tender. Laboratory data: The leukocytes numbered 6,700/cu. ml. The serum bilirubin measured 20 mg. per cent, and bilirubin was present in the urine. The temperature rose daily to 103.3° F. for three days, and thereafter remained normal. On April 5 (fourteenth day of disease), the serum bilirubin rose to 27.5 mg. per cent, and the cephalin-cholesterol flocculation was 4+. Thereafter jaundice regressed, and on April 19 (26 days after jaundice first was detected), the serum bilirubin measured 4.1 mg. per cent. The liver and spleen were still palpable when she was discharged home for further convalescence.

Case 4. A 62-year-old white male railroad employee was admitted to the Pennsylvania Hospital on March 8, 1946, with myocardial infarction and pulmonary edema. A total of 1,750 c.c. of pooled plasma (Pools Nos. 32, 33 and 35) was administered on the fifth, seventh and eighth hospital days. Recovery was uneventful. Four weeks after admission, a section of a penile lesion removed by biopsy showed epidermoid carcinoma, and roentgen-ray therapy was given during the succeeding five weeks. Eight weeks after admission, and 50 days after the first administration of plasma, the patient had nausea and epigastric distress, and jaundice was observed. Laboratory data: The serum bilirubin measured 4.1 mg. per cent, and the cephalin-cholesterol flocculation was 3+. During the next 12 days, jaundice increased until the serum bilirubin measured 26 mg. per cent, subsequently subsiding and disappearing on the thirtieth day of disease; the patient remained afebrile throughout this time. He was discharged improved three months after admission.

Case 5. A 68-year-old Italian male laborer had a two-stage prostatectomy for benign prostatic hypertrophy, February 8, 1947, and was given 500 c.c. of pooled plasma (Pools Nos. 63 and 64) at the time of operation. Recovery was uneventful, and he was discharged from the hospital. Forty-one days after the administration of plasma, the patient noted jaundice and light stools, epigastric fullness with flatulence, and mild discomfort in the right upper quadrant. He was re-admitted to the hospital on April 4, 1947, and physical examination revealed jaundice and slight tenderness in the epigastrium. The liver was palpable three to four fingers below the right costal margin. Laboratory data: The leukocytes numbered 12,500/cu. ml. The serum bilirubin measured 27.3 mg. per cent. The urine contained bilirubin; urobilinogen was present in the urine in a dilution of 1:100. The cephalin-cholesterol flocculation test was negative on admission but became positive shortly thereafter, and the thymol turbidity measured 9 units. The temperature did not rise above 99.6° F. Improvement was gradual, and jaundice diminished over a period of seven weeks. The

cephalin-cholesterol flocculation test became negative, and the thymol turbidity declined to 2 units. The gall bladder was not visualized in a cholecystogram, and no calculi were seen. The patient was discharged from the hospital recovered.

Case 6. A 65-year-old white retired carpet-cleaner had a prostatectomy for benign hypertrophy of the prostate, October 31, 1946, and 400 c.c. of pooled plasma (Pools Nos. 72 and 73) were administered postoperatively. He recovered uneventfully, and was discharged improved. About 10 weeks following discharge, the patient had anorexia, followed a week later by the appearance of dark urine and clay-colored stools. The following week (100 to 110 days after the administration of plasma), jaundice was observed. On re-admission to the hospital on March 14, 1947, physical examination revealed icterus of the skin, and mild tenderness in the right and left upper quadrants. The liver was palpable two fingers below the costal margin. Laboratory data: The leukocytes numbered 7,400/cu. ml. The serum bilirubin measured 24.4 mg. per cent, and the thymol turbidity measured 7 units. Bilirubinuria and increased urobilinogenuria were present. During his stay in the hospital, the temperature was normal. Anorexia and nausea improved, and convalescence was uneventful. The serum bilirubin declined, and jaundice disappeared after 80 days when the patient was discharged to complete his convalescence at home. At this time, the cephalin-cholesterol flocculation was 2+, and the thymol turbidity 5 units.

COMMENT

It is well known that no exact differential diagnosis can be made between *naturally occurring* infectious hepatitis and the *artificially induced* disease. Nevertheless, certain information may offer suggestive evidence to aid in making the distinction between them. It is apparent that resistance to the former increases sharply after 33 years, while the older age groups seem to be more susceptible to the latter form of disease. Thus, the occurrence of hepatitis at an appropriate interval after the reception of plasma parenterally strongly suggests the artificial transmission of the disease, particularly in older patients. In addition, the appearance of more than one case of hepatitis among patients receiving the same pool of plasma supports the presumption that such a pool is icterogenic.

The data recorded in this study are in general agreement with the results of similar investigations of others on the occurrence of homologous serum hepatitis after transfusions of pooled plasma and/or whole blood. The occurrence of hepatitis after transfusions of whole blood from individual donors was rare. The incidence of disease after transfusions of pooled plasma (0.96 per cent), as measured in a 19 month period from January 1946 to August 1947, is similar to that reported from another civilian general hospital in this country,¹⁶ but considerably lower * than the incidence reported in two larger surveys.^{17, 18} In the two latter studies, one in this country¹⁷ and one in England,¹⁸ the incidence of disease was recorded as 4.5 per cent and 7.3 per cent, respectively. The exact explanation of such differences is not known, and it is likely that they result from a combination

* After this manuscript was submitted for publication, Lehan et al. (Homologous serum jaundice, Brit. M. J. 2: 572, 1949) reported an incidence of 11.9 per cent homologous serum jaundice among the recipients of large-pool plasma in England.

of factors including variations in completeness of follow-up of recipients, number of donors contributing to pools, susceptibility of host, strain of virus, and size of infecting dose of virus.

Although the incidence of disease after transfusions of pooled plasma was low in this study, it has been emphasized that the *potential* icterogenic capacity of the 64 pools of plasma was high, ranging from 8 per cent to 16 per cent. Thus, under different conditions possibly involving, among other things, increased virulence of virus and decreased resistance of host, the incidence of artificial transmission of the disease may be subject to wide variations. This is in accord with the experience of the past few years in relation to the different icterogenic capacities of various pools of human serum or plasma which have been implicated as causing homologous serum hepatitis.

At present, there is no method known to detect hepatitis virus in the blood of donors, and it has been emphasized that the methods of lessening the artificial transmission of disease include diminishing the number of donors contributing to pools of plasma, and reserving the use of plasma for patients actually requiring it. Recently, Blanchard et al.¹⁹ demonstrated that one strain of homologous serum hepatitis virus may be inactivated in plasma by exposure to ultraviolet radiation by a method which is commercially practicable on a large scale. This suggests that some such procedure may eventually be generally employed.

SUMMARY

1. The experience of a civilian general hospital with homologous serum hepatitis during a five year period from 1942 to 1947 is presented.
2. Fifteen patients contracted the disease after transfusions of pooled plasma and/or whole blood, and three of them died. Fourteen patients (93 per cent) received plasma, or blood and plasma. Only one patient received blood alone.
3. During the 19 month period from January 1946 to August 1947, six out of 621 (0.96 per cent) recipients of pooled plasma contracted homologous serum hepatitis.
4. Although the incidence of disease was low, the potential icterogenic capacity of the 64 pools of plasma made during this time was high, since a minimum of 5 (8 per cent) and a maximum of 10 (16 per cent) were presumably infected with hepatitis virus.

The author is indebted to the following physicians for the privilege of utilizing the case records of certain of the patients included in this report: Drs. John B. Flick, Garfield G. Duncan, Maurice S. Sackey, Leonard W. Parkhurst, Perry S. MacNeal, Joseph B. Vander Veer, and Lawrence S. Carey.

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CHRONIC PULMONARY GRANULOMATOSIS IN RESIDENTS OF A COMMUNITY NEAR A BERYLLIUM PLANT: THREE AUTOP- SIED CASES *

By CHARLES CHESNER, M.D., *Lorain, Ohio*

INTRODUCTION

THE purpose of this paper is to alert the physicians to a chronic type of pulmonary disease of high fatality occurring in individuals living in a community where beryllium is produced.

In 1943 and again in 1945, Van Ordstrand^{1,2} and associates described cases of acute beryllium poisoning in workers in plants producing beryllium, its compounds and alloys. One of the papers² recorded the autopsy findings in five fatal cases. The signs and symptoms of the acute beryllium intoxication began while the patients were actively engaged in working with beryllium and, in the non-fatal cases, cleared up when the worker was removed from the environment.

In 1946, Hardy and Tabershaw³ coined the term "delayed chemical pneumonitis" to describe cases of chronic pulmonary disease occurring in workers exposed to beryllium compounds in a fluorescent lamp factory. The onset of the disease in most cases was delayed from varying periods of time up to three years after the individual left the occupation. In 1947, Hardy^{4,5} mentioned three cases of what appeared to be true examples of delayed chemical pneumonitis in individuals who were not workers. Two lived geographically very close to the building where the fluorescent powders were being handled. The third was a mother who nursed a sick working daughter who died after two years of a severe course of delayed chemical pneumonitis. Two of the "neighbor" cases died and were autopsied. The findings were similar to those in the worker group in that area.

In 1946, and twice in 1948, autopsies were performed on individuals in this community in which the chief findings were a diffuse chronic pulmonary granulomatosis. None of these individuals was ever employed in the local beryllium plant. The clinical, roentgenological, and autopsy disclosures were similar to those described by Hardy,^{4,5} Hardy and Tabershaw,³ Gardner,⁶ Martland and associates⁷ and Higgins,⁸ as occurring in workers believed exposed to beryllium or its compounds. The cases to be described here have also been included in a recent comprehensive clinical article by DeNardi⁹ and associates.

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From St. Joseph Hospital, Lorain, Ohio.

CASE REPORTS

Case 1. This 38-year-old white female first noted symptoms in January 1944, approximately 30 months before her death July 16, 1946. Following a cold January 1944, she noted persistent weakness, slight cough, exertional dyspnea and slight weight loss. There were no chills or fever. The past history revealed no previous cardio-respiratory disease. She was delivered of normal children August 16, 1943 and April 13, 1945.

Occupational History: There was no direct occupational history. She never worked in the beryllium plant, but lived approximately two blocks from the plant until August 1945, when she moved to her last address about one and one-half miles from the plant. She first noted symptoms in January 1944 on "foggy" and "dreary" days when she could see and smell fumes from the plant.

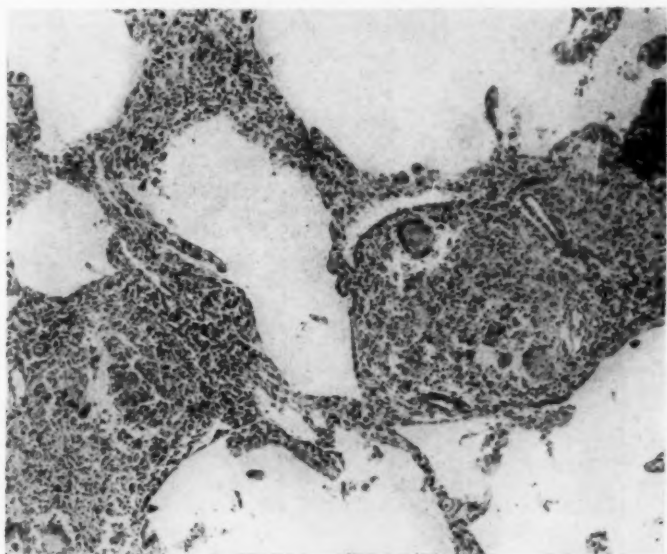


FIG. 1. *Case 1.* Lung ($\times 158$). Nodular distribution of the lesion with diffuse spread in the interalveolar septa. Endothelial type cells, giant cells, and a polymorphous round cell infiltrate compromise the nodule. The overlying alveolar septa are lined by a cuboidal epithelium. An inclusion body is seen in one corner.

Laboratory findings September 1944 showed an essentially negative urine, 94 per cent hemoglobin, 4.7 million red blood cells per cu. mm. and 8,950 white blood cells per cu. mm. with 76 polys, 14 lymphocytes, 5 monocytes, 4 eosinophiles and 1 basophile. The roentgenogram at this time showed increased bronchovascular markings in the first interspace on the right side with negative findings on the left side. She was investigated for minimal tuberculosis.

She was seen by her family physicians frequently during the period of her illness and repeated examinations showed an increasing loss of weight, increasing cough and progressive and marked dyspnea with substernal pain.

She was seen at the Cleveland Clinic in October, 1945. The patient stated that she had lost 20 pounds during the preceding summer. The cough was more pronounced, dyspnea was marked and there was substernal pain on respiration. The temperature was 98.2° F., pulse 96 and blood pressure 128/98 mm. Hg. There was early clubbing of the fingers and toes and slight cyanosis of the nail beds. The thyroid gland was slightly larger than normal but there were no clinical signs of hyperthyroidism. The heart was not enlarged, rhythm was regular. The peripheral venous pressure was elevated with enlargement of the jugular veins almost to the



FIG. 2. Case 1. High ($\times 450$) power view of lung showing several inclusion bodies.

angle of the jaw in the sitting position. The urine was negative, the hemoglobin 91 per cent and the white blood cells 8,300 per cu. mm. The Kahn and Wassermann tests were negative. A roentgenogram showed prominence of the pulmonary conus. There was a diffuse, ground glass-like infiltration throughout all lung fields. The electrocardiogram showed right axis deviation with inversion of the T-wave in Lead III and precordial lead. These findings were consistent with the presence of right ventricular strain.

The first record of a roentgen-ray film was in September 1944 and the findings

were as recorded above. Comparison films on November 1944 and July 1945 showed no significant changes. The next film was taken at the clinic October 1945 and the findings were listed above. Several small areas of calcification were noted in the hilar area, and the left border of the heart presented a mitral contour.

The patient was seen on June 7 and 15, 1946. Chest examination revealed fine crepitant râles at the base with "wheezy" râles over hilar areas. Chest expansion was limited. The liver margin was at first 2 cm. below the costal margin and a week later 6 cm. below the costal edge. There was dependent edema of the ankles and feet. The patient was cyanotic at rest and complained of marked weakness and dyspnea.

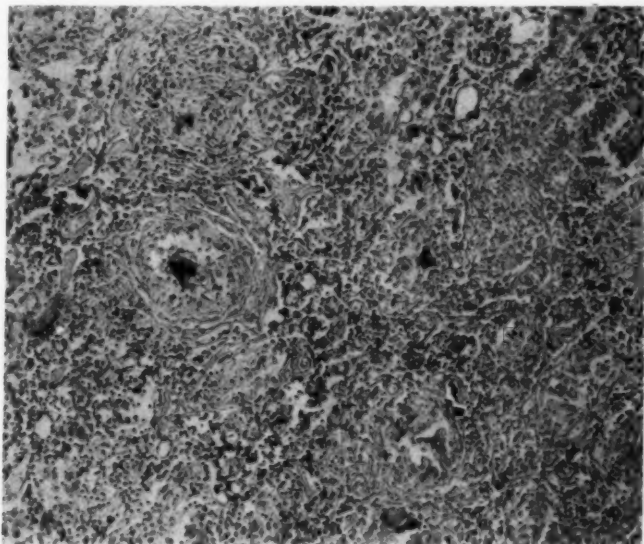


FIG. 3. Case 1. Lymph node ($\times 158$) showing the characteristic nodules. There is considerable fibrosis. Giant cells and inclusion bodies are seen.

During the length of illness, there was no appreciable temperature rise and the blood pressure varied between 110-120/70-80 mm. Hg. The weight was 103 to 105 pounds normally and dropped to 90 pounds a few months before death. The pulse ranged between 84 at the start of the illness and 120 a few months before death.

Autopsy: Only the pertinent findings will be recorded. The patient was about 62 inches in body length with an approximate weight of 110 lbs. The abdomen contained one to two liters of a thin, clear, amber colored fluid. The liver extended three fingers' breadth below the right costal margin. The pleural cavities were filled with a thin clear fluid. The heart weighed about 320 grams and showed dilatation of the tricuspid valve with hypertrophy and dilatation of the right ventricle. The right ventricle was 8 mm. thick and the left ventricle 14 mm. Both lungs were large, rubbery, and sub-crepitant in consistency. The hilar lymph nodes were enlarged up to 25 mm. and were soft and anthracotic. The spleen was enlarged to four or five times its normal size and weighed approximately 550 grams. On section the pulp was firm and cyanotic. The liver was enlarged and estimated to weigh between 1,900 and

2,000 grams. The cut surfaces were pale tan in color with blush dots scattered throughout. There were no other significant gross findings.

Microscopic Sections. Lungs: Sections showed a diffuse and focal type of granulomatous lesion, present in all lung fields. The nodules were of miliary size and larger, with accumulations of cells in the inter-alveolar walls. There was distortion of the alveoli leading in some areas to complete obliteration of the alveolar spaces, with compensatory emphysema at other points. The nodules presented an admixture of large cells of the endothelial type with oval nuclei and abundant cytoplasm, with lymphocytes, mononuclears and giant cells. The large endothelial-like cells tended to congregate in the center of the lesion. The lymphocytes and mononuclears lay in the greatest number at the periphery, but also intermingled with the endothelial-like cells. Giant cells of the foreign body and Langhans types were present in fairly large numbers. There was no caseation. Within a number of these giant

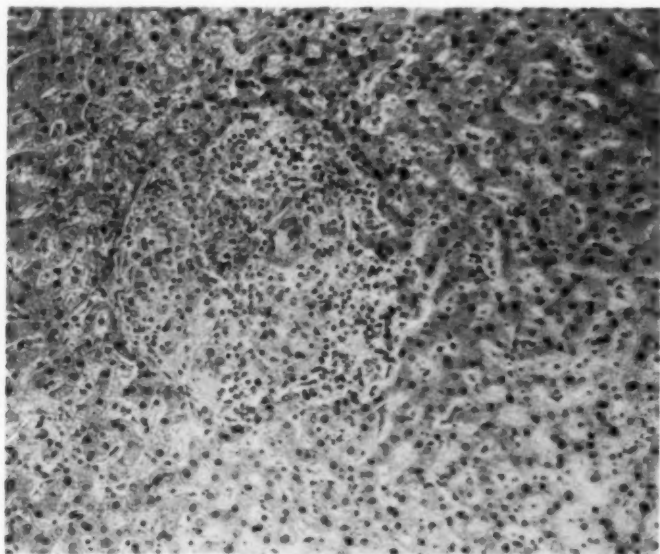


Fig. 4. Case 1. Liver ($\times 158$) showing a granulomatous nodule in the portal tract.

cells there were numerous bodies which stained black with hematoxylin and eosin. These bodies assumed multi-form shapes. They frequently appeared in elongated intertwining skein formations. They were seen as condensed black masses with a diameter of three to six times that of a lymphocyte. They were also seen as solid masses surrounded by a clear zone with a peripheral arrangement of concentric dark-staining rings, resembling a snail. Sometimes the dark-staining core was not present. The nodules showed little to no fibrosis. In between the focal lesions there was a diffuse cellular reaction with little or no fibrosis. Lymphocytes and monocytes predominated. The alveoli surrounding a number of the focal and diffuse lesions were lined by a cuboidal type of epithelium. There was slight fibrosis of the pleura. Stains for acid fast bacilli and bacteria were negative.

Spleen: The pulp was flooded with red blood cells.

Liver: The sinusoids were distended with blood, mainly in the central segments of the lobule. The cells showed evidence of parenchymatous degeneration. The portal canals presented occasional miliary type nodules with a preponderance of endothelial-like cells, eosinophiles, round cells and an occasional giant cell of the foreign body type.

Lymph Nodes: The lymph nodes were largely replaced by the same type of nodular lesion seen in the lung. The nodules were composed of a predominance of endothelial-like cells and numerous giant cells of both the Langhans and foreign body type. There was a patchy fibrosis and hyalinization. Inclusion-type bodies were seen in large numbers within the giant cells. Acid fast and bacterial stains were negative.

Final Diagnosis: Diffuse bilateral granulomatous pneumonitis; granulomatous involvement of hilar lymph nodes and liver; passive congestion of liver and spleen, early; bilateral hydrothorax and ascites; marked hypertrophy and dilatation of entire right heart; mild chronic cholecystitis; parenchymatous degeneration of the viscera; compensatory emphysema.

Beryllium Analysis (Kettering Laboratories): (1) Lung—nil or 0.00008 microgram Be/100 gm.; (2) Formalin in which tissue was sent—nil. (Rochester University Laboratories): (1) Lung—0.05 microgram/100 gram; (2) Formalin—nil.

Further information about this case is recorded under "Toxicology."

Case 2. This 26-year-old white female was first seen August 1946 with the chief complaint of cough and steady loss of weight. She claimed to have lost 11 lbs. in the past six months. Extreme dyspnea was first noted June 1946. Her past history was essentially negative except for two normal pregnancies in 1942 and 1944.

Occupational History: There was no history of direct or indirect chemical contact. She lived between one-half and three miles from the beryllium plant during the years 1936 to 1948. There were 10 addresses given for this period, the closest being approximately one-half mile from the beryllium plant. This was in 1941. A next door neighbor at one of these residences was a sweeper at the beryllium plant. He used to take home bags from the plant and shared them with the patient. The bags were the original containers for the beryllium ore. The patient used them as dish cloths.

Physical Examination: August 12, 1946 revealed a normal temperature, pulse 100, and blood pressure 110/86 mm. Hg. There were a few fine crepitant râles posteriorly. The vital capacity was approximately 70 per cent of normal. The findings were otherwise negative. Laboratory studies at this time included urinalysis, blood count, blood sugar and Wassermann and Kahn tests and there were no significant findings. A roentgenogram of the chest at this time showed accentuated hilar shadows, especially on the right side with a diffuse granular appearance of all lobes. A tentative diagnosis was made of pulmonary lymphoblastoma. Roentgen-ray therapy of the chest was carried out (September 1946) with no appreciable improvement. A second course of radiation therapy was given in April and May 1947. In June of 1947, the patient developed purpuric areas of the skin and mucous membranes and a rather severe uterine hemorrhage. Laboratory findings at this time revealed a hemoglobin of 13.5 grams per 100 c.c., a red blood count of 5.9 millions per cu. mm. and a white blood count of 5,250 thousands per cu. mm. with 60 per cent polys, 9 non-segmenters, 15 monocytes, 12 lymphocytes and 3 eosinophiles. The platelets were reduced to 10,000 per cu. mm. The coagulation time was 12 minutes, the bleeding time was over 15 minutes and there was no clot retraction in 24 hours. The prothrombin time was 16 seconds.

Following the second course of irradiation therapy there was some clearing of the lung fields (June 1947) but no clinical improvement. The platelet count remained at the same low level on repeated examinations in July and August 1947—

between 10 to 200 thousands per cu.mm. A roentgenogram in November 1947 showed evidence of considerable progression of the disease.

The clinical course was downward with anorexia, weight loss and dyspnea, the latter becoming so pronounced that she was forced to remain in bed in Fowler's position during the last few months of her illness. She remained afebrile.

The last physical examination was done February 16, 1948, one day before death. The patient was in extreme respiratory distress with cyanosis at rest and clubbing of the fingers. There were fine and coarse, moist râles heard throughout the chest. The liver and spleen were palpable. The heart dullness was beyond normal limits in both directions. There was dependent edema of the feet and ankles.

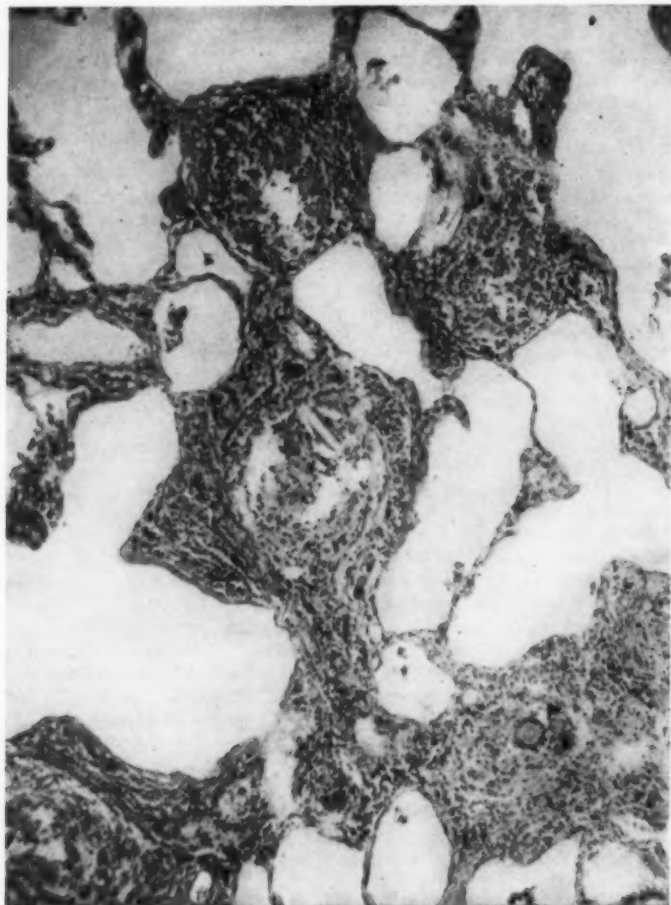


FIG. 5. Case 2. Lung ($\times 117$) showing typical nodular lesions with a polymorphous cellular infiltrate, fibrosis and round cells. The center nodule presents suspicious crystalline-like substances. The adjacent alveoli are emphysematous.

Autopsy: Only the pertinent findings will be recorded. The patient was 64 inches in body length and in a poor state of nourishment, weighing approximately 100 lbs. The midline fat measured 0.5 to 1 cm. in thickness. The liver extended four fingers'-breadth below the right costal margin. There was no fluid in either pleural sac. There were mild fibrous adhesions covering the mid-portion of both lungs. The heart weighed 265 grams and showed no significant changes. Both lungs were similar in appearance. They were fairly large and heavy, and covered by a fibrinous membrane, especially over the lower lobes. The lower lobes and the lower halves of the upper lobes varied from solid to rubbery in character. The upper lobes in the region of the apices presented a polycystic appearance, the spaces measuring from 1 to 10 mm. in diameter and containing only air. The hilar lymph nodes measured from 5 to 20 mm. in diameter and were soft and dirty-gray color. The spleen weighed 150 gm. and the pulp was firm and deep red in color. The liver weighed 1,250 gm., and the cut surfaces showed alternate pale tan and blue markings. The other organs showed no significant changes.

Microscopic. Lungs: The pleura was tremendously thickened with fibrin, adult fibrous tissue, organizing fibrous tissue, increased vascularity, and small numbers of round cells. The parenchyma presented a uniform involvement by nodules within the alveolar walls, and an intervening diffuse cellular reaction between nodules. The diffuse type of reaction predominated. The nodules were composed of endothelial-like cells with large oval vesicular nuclei and abundant clear cytoplasm, lymphocytes, monocytes, and giant cells of the foreign body and Langhans types. Fibrosis was considerable and appeared to start around the periphery of a nodule and work its way inward. Giant cells were numerous. There was no caseation. The diffuse granulomatous type of reaction was marked, with a polymorphous cellular exudate, of the round cell type, and considerable fibrosis. The alveoli were covered by endothelial cells, especially in the areas of diffuse granuloma. Many alveoli showed a compensatory type of emphysema and some reached huge proportions. There was edema fluid and mononuclears within the alveolar spaces, with occasional giant cells. A few of the smaller arterioles had adherent blood clot within the lumen.

Spleen: The sinusoid linings were prominent and epithelial-like in character with dilatation and contained red blood cells. The pulp cords were broadened with reticulum cell hyperplasia and round cell infiltration.

Liver: Advanced chronic passive congestion with parenchymatous degeneration.

Lymph Nodes: The normal architecture was almost completely replaced by nodular lesions of miliary size. There was predominance of the endothelial-like cells, infrequent giant cells, and fibrosis and hyalinization. The fibrosis began at the periphery of the nodule and extended inwards and between nodules, involving large segments in a patchy fashion.

Marrow: Hyperplasia of the myeloid tissue.

Final pathologic diagnosis was chronic bilateral granulomatous pneumonitis with hilar lymph node involvement; chronic passive congestion of the viscera (acid fast and bacterial stains were negative).

Beryllium Analysis: The results from the University of Rochester Laboratory were as follows:

Lung No. 1	0.07 microgram per 100 gm.
Lung No. 2	0.08 microgram per 100 gm.
Liver	Less than 0.05 microgram per 100 gm.
Kidneys	Less than 0.07 microgram per 100 gm.
Formalin	Less than 0.01 microgram per 100 gm.

Kettering Laboratory:

Lung	1.93 micrograms per 100 gm.
Liver	1.48 micrograms per 100 gm.
Lymph nodes64 micrograms per 100 gm.
Spleen017 microgram per 100 gm.

Case 3. This was the second admission of this 8-year-old white female. Her previous admission was July 5, 1948. She was apparently in good health until March, 1947. Following an attack of measles, she began to lose weight and had a spasmodic cough productive of a thick, yellow sputum. The local school teacher noted that the child was unable to walk up one flight of steps without a great deal of exertion. A roentgenogram taken at the local sanatorium on December 1947 showed a diffuse granular infiltration of both lungs with no definite evidence of tuberculosis. She was examined in Cleveland on June 26 and on July 2, 1948, and was found to be acutely ill, weak and cyanotic, with clubbed fingers. There was a 75 per cent left pneumothorax. Following her return from the Cleveland Clinic she was hospitalized here for the first time because of weight loss and pulmonary distress.

Contact History: From June, 1941 to April, 1947, she lived approximately one mile east of the beryllium plant. The family then left town. Her father had worked at the beryllium plant for one year from 1937 to 1938. An uncle lived with the family from August 1946 to March 1947. This man was suffering from chronic granulomatous pneumonitis at this time. He worked at the plant for six weeks during the summer of 1941.

Past History: Chickenpox at four years of age. Measles at six and one-half years of age.

Family History: Father and mother alive and well. A paternal aunt died of pulmonary tuberculosis at 33 years of age.

Laboratory Work Prior to Admission: Sputum and gastric lavage were negative for tuberculosis as was a patch test. On March 15, 1948, the red blood cells were 5.03 millions per cu. mm., hemoglobin 14 grams per 100 c.c. and white blood cells 12,600 per cu. mm. with 70 per cent polys and 28 per cent lymphocytes. The sedimentation rate was 10 mm. per hour. Beryllium urinalysis done at the University of Rochester, showed less than 0.01 microgram of beryllium per liter.

Roentgenograms Prior to Admission: Roentgenograms were taken December 1947, March 1947 and May 1948. All showed the same type of diffuse bilateral infiltration with no evidence of active tuberculosis. Films on July 1948 showed 75 per cent left pneumothorax.

Physical examination on first admission, July 5, 1948, revealed a markedly emaciated, poorly developed and dyspneic white child. The height was 46 inches and weight was 37 lbs. There was marked acrocyanosis with clubbing of all fingers and toes. There was no evident adenopathy. The excursion of the chest was diminished. Breath sounds were harsh throughout. Fine crepitant râles were audible over both lung fields. The heart was normal to percussion and auscultation and the rate was rapid. The liver edge was palpable just below the costal margin.

Laboratory Work: Urinalyses on repeated occasions were negative except for slight traces of albumin. The red blood cells varied from 4.80 to 5.29 millions per cu. mm. and hemoglobin varied from 100 to 106 per cent. The white blood cells varied from 10.8 to 15.2 thousands per cu. mm. with a differential count of 2 to 10 stab forms, 66 to 82 polys, 1 to 3 monocytes and 13 to 24 lymphocytes. A glucose tolerance test on August 31, 1948 showed a fasting blood sugar of 92 mg. per cent going up to 109 in one-half hour and 207 in one hour and a quarter. The urines were all negative for sugar.

Further X-Ray Studies: A film on July 10, 1948 showed a 40 per cent collapse



FIG. 6. *Case 3.* High power view of the gross lung. Pin-head sized whitish dots are diffusely scattered throughout the cut surfaces.

and on July 20 a disappearance of the pneumothorax. On August 5 and 30, there was reëxpansion of the left lung. The granular infiltrate showed no change from previous films.

Course: The patient was given penicillin 10,000 units every three hours and penicillin inhalation during her first admission. She was discharged slightly improved. She was re-admitted July 29, 1948 in marked respiratory distress and was given continuous oxygen, penicillin by injection and inhalation and streptomycin in

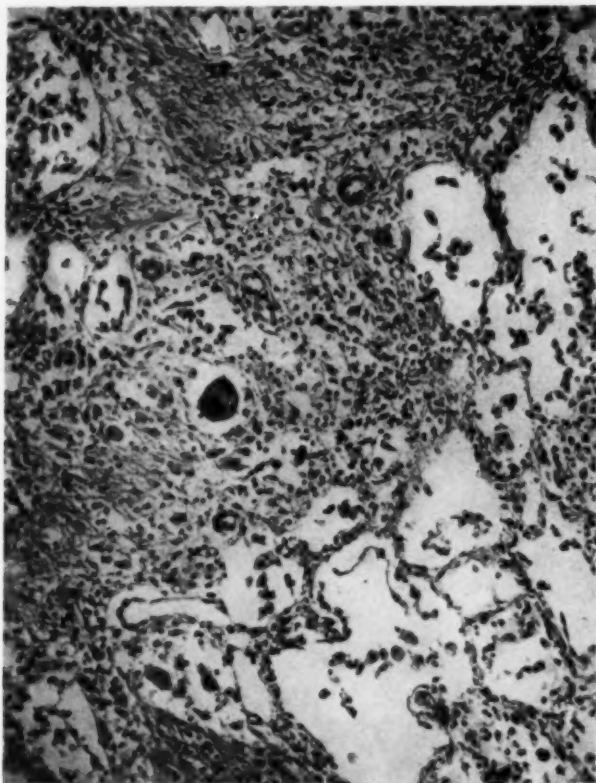


FIG. 7. Case 3. Lung ($\times 150$) showing a slightly higher power view of the nodular and diffuse type of infiltrate.

adequate doses. The temperature charts for both admissions revealed irregular rises in temperature to 101° F. The pulse rate ranged between 100 to 160 per minute and the respiratory rate between 30 to 60 per minute. She died on September 4, 1948 of a superimposed acute terminal pneumonia, approximately one and one-half years from the onset.

Autopsy: The patient was in a cachectic state and measured 44 inches in body length. There was practically no subcutaneous fat. The liver was enlarged four

fingers below the arch of the rib. When the chest was opened no fluid or adhesions were seen. The heart weighed 100 gm. The left ventricle measured 10 mm. in thickness and the right ventricle 4 mm. The chambers were somewhat dilated. The right lung was heavy and showed areas of apparent consolidation in the lower portion of the right upper lobe and in the right lower lobe. The remainder of the right lung was granular to palpation. The pleura was smooth. The left lung showed an opaque, gray, thickened pleura. The bronchi were patent throughout. The hilar lymph nodes were enlarged and had a yellow gelatinous appearance. The liver weighed 650 grams. The organ was flabby and reddish brown in color, but with decreased resistance and brown slightly bulging surfaces. The spleen weighed 90 grams. The Malpighian bodies were large and there were a few gray nodular lesions that measured up to 2 mm. in diameter. The other organs showed no significant changes.

Microscopic. Lungs: The pleura was thickened with fibrosis and an increase in small blood vessels. The parenchyma showed a diffuse and nodular type of granulomatous lesion. The nodular lesions were miliary in size or larger, occurred in the interalveolar septa, and presented considerable fibrosis and hyalinization intermingled with lymphocytes, mononuclears and giant cells. The latter were multinucleated and of the foreign body and Langhans types. There were occasional large focal hyalin plaques with surrounding fibrosis, round cell infiltration and giant cells. Between the nodular areas there was a diffuse granulomatous reaction and a polymorphous round cell infiltration and considerable fibrosis. There was very little lung tissue left. The alveoli that were patent contained a cellular exudate with a predominance of large mononuclears with pale staining cytoplasm. Most of the overlying alveoli were covered by a layer of cuboidal epithelium. The nodular lesions with or without fibrosis or hyalinization were prominent even in the midst of diffuse granulomatous reaction. Within the giant cell, dark staining "inclusion bodies" were occasionally seen. There were areas of compensatory emphysema. The larger bronchi showed vascularity and round cell infiltration.

Spleen: The sinusoids were dilated and filled with blood, with a prominent glandular-like endothelial lining. The pulp was congested. There was a proliferation of endothelial cells. The follicles and germinal centers were prominent.

Liver: Congestive changes were present. An occasional nodule was noted in the portal canals consisting of lymphoid, polynuclear and endothelial cells.

Lymph Nodes: Sections showed replacement of large segments of the lymph node by a nodular type of lesion with a preponderance of endothelial-like cells and giant cells. There was early peri-nodular and intra-nodular fibrosis with laying down of collagen within and between nodules to form dense hyaline areas of varying size and totally irregular distribution throughout the node. Some segments showed nodular lesions with minimal or no fibrosis, while other areas on the same slide showed large dense bundles of hyaline tissue. Giant cells were present in large numbers. Dark-staining intracellular (within giant cell) bodies were found in small numbers, but apparently more numerous than in the lung.

Final Pathologic Diagnosis: Bilateral chronic granulomatous pneumonitis with hilar lymphadenitis; granulomatous involvement of liver; right ventricular hypertrophy and dilatation; chronic passive congestion of viscera (acid fast and bacterial stains were negative).

Beryllium Analysis (by Dr. Frank Dutra of Kettering Laboratory):

Lymph node	0.665 microgram per 100 gm.
Lung	0.237 microgram per 100 gm.
Kidney	nil or less than 0.02 microgram per 100 gm.
Spleen	nil or less than 0.02 microgram per 100 gm.
Liver	nil or less than 0.008 microgram per 100 gm.

BERYLLIUM: EXTRACTION AND USES

Beryllium is one of the lighter metals belonging to the same chemical group as magnesium and calcium. It is usually found as an inert ore, beryl, a double silicate of beryllium and aluminum.

Extraction of beryllium is difficult because of the refractory nature of beryl and its comparative inertness towards acids and alkalies. It is extracted under high temperatures from the inert ore by a method involving the use of concentrated acids and fusion. Fumes and dust of the by-products are present at various stages of the processing.

Its uses are manifold. It is a strategic metal and its availability is governed by priority regulations. The alloy of beryllium and copper represents its most important use. It has an astonishing fatigue resistance. Springs made from this alloy are said to retain elasticity almost indefinitely even in atmospheres that are highly corrosive to steel springs. It is used in diaphragms of altimeters, and in gasoline and oil pipes in airplanes where vibration is excessive. The electrical conductivity is higher than that of steel. It is used as a target for high voltage deuterons, producing neutron beams of great intensity, and has therefore found its place in atomic energy manufacture. It was used in the Manhattan Project. It is also used in fluorescent powders, radio tubes, neon sign tubing and incandescent lamps.

OCCUPATIONAL HISTORY AND EXPOSURE

Eleven cases of delayed chemical chronic pneumonitis were observed in this area. Ten of these histories were incorporated in a recent paper by DeNardi and his associates.⁹ The clinical material in this report was made freely available to me.

Seven of the 11 did not work with beryllium or its compounds. There were three deaths, all from the neighborhood group, and three autopsies. Four of these seven cases lived within a radius of 300 meters from the beryllium plant for a period of one to four years. There was one death in this group. One case lived about three miles from the beryllium plant where her husband was employed for an eight week period. She did not handle his work clothes and denied the possibility of contamination. Two lived about one-half mile from the plant for periods of one to five years. There were two deaths in this group. A worker case of chronic chemical pneumonitis lived at one of these homes for a six month period (Case 3). The other member in this fatal group (Case 2) lived next door to a sweeper in the beryllium plant and used bags brought home from the plant for dish cloths. One of her two children is being followed up at the present time for possible chronic pulmonary granulomatosis.

Of the four worker cases, two left because of acute tracheo-bronchitis. There were no deaths in the worker group. One was employed at the beryllium plant for eight weeks in 1941 and left because of acute tracheo-bronchitis. His first symptoms were in January 1946. The second worked

for one month from April 30 to May 30, 1945 and developed acute respiratory symptoms. He returned to work July 9, 1945 and again developed acute symptoms. He was dismissed after clinical cure in September. The onset of the chronic disease was October 1947. The third worked in the plant for six weeks in the summer of 1941. His earliest symptoms were in December 1944 while serving in the army. The fourth individual was employed in the laboratory of the beryllium plant from November 1943 to February 1944, a total of 12 weeks. Her chronic illness dated from August 1946.

Preliminary sampling of the air in the proximity of the plant revealed a minimal contamination for only a short distance, and there was a disproportionate ratio between the magnitude of exposure in the plant environment and that in the immediate vicinity of the plant.⁸ A sampling of the air for beryllium in most of the city was recently done in a survey by the Atomic Energy Commission. The reports of the findings are not yet available.

In summary, there were four worker cases who developed the chronic type of occupational pneumonitis. This represented but a small portion of the total number employed. The onset of the disease was delayed for periods of 27 months to four and one-half years after the last exposure. The period of employment in the beryllium plant varied from six to 12 weeks. As for the neighborhood cases, the duration and the extent of exposure were even more uncertain.

The low incidence, spotty distribution and the lack of relationship of the severity of the disease to the degree of exposure was in accord with reports from the literature. Hardy^{4,5} analyzed 36 cases in an industry employing about 1,000, including three neighborhood cases. These individuals were engaged at their work for periods of time varying from eight months to eight years. Some developed symptoms while at work but in most the onset was delayed from three months to three years after leaving the industry. Hardy was unable to correlate the length and intensity of exposure with either the time of the onset or the severity of the disease. Gardner⁶ analyzed approximately 100 cases of proved and possible sarcoid in his files from industries associated with a potential beryllium hazard. He also commented on the low incidence rate and the apparent lack of relationship of the disease to the degree of exposure. This is in distinct contrast to the other pneumoconioses wherein the incidence of the development of the disease was far greater among those having the greater exposure. He thought that perhaps the beryllium was not the only factor involved and that beryllium might act with some other factor nature unknown, to initiate the pathologic process. Martland⁷ discussed the possible reasons for the low incidence rate. These were:

1. The occupational histories were not complete; the job details involved were listed in a vague manner.
2. The number of people intimately exposed to beryllium was perhaps lower than the total in the industry.

3. The intelligence and carefulness of the worker in protecting himself was an important factor.

4. The integrity of the respiratory tract at any given time was important in determining the individual susceptibility.

ETIOLOGY

Studies of the sputum by smear or culture for a predominating bacterium, or fungus, and for tubercle bacilli were uniformly negative. Gardner⁶ was unable to produce the disease in animals by injection or inhalation of zinc beryllium silicate, beryllium oxide or other mixed phosphors recovered from old lamps. Hyslop and associates,¹⁰ working at the National Institute of Health, found that beryllium itself was not toxic but that the toxicity was due to the acid radical in the extraction of beryllium. They were unable to reproduce the chronic type of disease. Hardy^{4,5} listed the possible predisposing factors in her 36 cases. There was a history of chronic respiratory disease in seven, pregnancy before the onset of the disease in nine and war fatigue in three. The only common factor in all these cases was an occupational background where beryllium was used, or residence near a beryllium plant. None of the cases of acute chemical pneumonitis in this community (Lorain) has developed the chronic form of the disease.¹¹ Two of the worker cases suffered from acute tracheo-bronchitis but not pneumonitis.^{1,2}

CLINICAL PICTURE

The clinical picture is discussed in detail by Hardy and Tabershaw,³ Hardy,^{4,5} Higgins⁸ and DeNardi and associates.⁹ The onset was insidious and the patient usually failed to seek medical advice in the early months. The disease usually started with a mild cough, productive or non-productive, following an acute respiratory upset. Concomitant with the cough there was exertional dyspnea. Anorexia, nervousness and weight loss were constantly present. Acrocyanosis and clubbing of the fingers were late features. Fever was not characteristic. On physical examination, the patients were cachectic and dyspneic. The vital capacity was greatly reduced. Chest expansion was limited and substernal pain was experienced at the height of inspiration. Breath sounds were normal in character throughout. At times, fine crackling râles were heard in the hilar region.

LABORATORY STUDIES

DeNardi and associates⁹ did complete blood counts, urinalysis, sedimentation rates, non-protein nitrogen, blood sugar and serum albumin-globulin ratios on all cases. The results were not revealing. Hardy⁴ found slightly elevated blood globulin, calcium and alkaline phosphatase levels in a few of the most seriously ill. There were uniformly negative sputum smears, cultures and skin tests for acid fast infection. Blood and sputum studies for other organisms were negative.

X-RAY STUDIES

Chest roentgenograms were characteristic in all cases and helped clinch a doubtful diagnosis. There was basic agreement by the various authors^{3, 8, 9, 12} as regards the chest roentgenogram. Sosman and Wilson, quoted by Hardy and Tabershaw,³ described three stages:

1. A fine diffuse uniform granularity, like sandpaper, with normal hilar markings.

2. A diffuse reticular pattern on the granular background with fuzzy hilar shadows.

3. Distinct nodules, from 1 to 5 millimeters in size, resembling a snow storm, evenly distributed. The hilar shadows fuzzy. The pulmonary artery may become prominent. No cavitation.

PATHOLOGY

The basic pathology was a diffuse intra-alveolar nodular granulomatous lesion which involved all lung fields at an early stage. The nodules were composed of a preponderance of large endothelial-like cells with an addition of intermingled plasma cells, mononuclears and lymphocytes. There was no caseation at any stage. Giant cells of both the foreign body and Langhans types were noted in fairly large numbers in all cases. Inclusion bodies in the giant cells were seen in large numbers in Case 1, not at all in Case 2 and infrequently in Case 3. They were present mainly within the giant cells but were also noted extra-cellularly in the granulomatous areas. They assumed various forms. They appeared as long, narrow, intertwining skein-like bodies. Many assumed a snail-like formation, with concentric dark staining areas surrounding either colorless or compact black staining central cores. The shape varied from a rounded body to a distorted, stretched out, elongated one. These bodies stained black with hematoxylin and eosin stain. The alveoli overlying the granulomatous areas were lined by a cuboidal type of epithelium. This feature is seen in other chronic inflammatory lesions of the lungs.

Spread apparently occurred locally by expansion or conglomeration of nodules, or in a more diffuse fashion throughout the alveolar septa. Regardless of the extent of the diffuse spread, the focal lesions remained prominent. The diffuse reaction was at first a polymorphous cellular one of the round cell type with fibrosis and hyalinization occurring at a later stage. In Case 2 there were a number of nodules with advanced peripheral fibrosis and little or none within the nodule, so this might represent an early stage in the fibrosing process. In Case 1, there was little or no fibrosis and the focal type of lesion was outstanding. In Case 2, the diffuse granulomatous reaction was predominant with early fibrosis. In Case 3, fibrosis was the farthest advanced with the formation of isolated large focal hyalin patches.

Hilar lymph nodes were implicated in the granulomatous process in all cases. The pathology was similar to that found in the lungs. The liver was involved in two of the cases. This would indicate spread by the blood stream. Gardner⁶ mentioned extension to the spleen. The spleen was not involved in any of these cases. There was no other visceral involvement. Acid fast and gram bacterial stains were negative.

Other constant findings were right cardiac dilatation and hypertrophy, chronic passive congestion, and compensatory pulmonary emphysema, which was marked in Cases 2 and 3.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The clinical diagnosis was based upon an occupational history of exposure to beryllium or residence in a community where beryllium was produced plus a typical clinical picture of insidious onset with cough and exertional dyspnea. The symptoms progressed in spite of changes of environment. The course was usually afebrile. Cachexia and weight loss became prominent. The occupational exposure may have been brief and the onset of the disease may have been deferred for a long period of time after the individual left the industry or environment. Roentgen-ray findings of a diffuse ground glass appearance with superimposed small nodules were characteristic. According to DeNardi,⁹ the symptomatic onset of the disease preceded the roentgenographic findings by several months.

The differential diagnosis is dealt with in the papers by Hardy,^{4,5} Gardner,⁶ Martland,⁷ and DeNardi,⁹ and Pascucci.¹² In the differential diagnosis, Boeck's sarcoid, miliary tuberculosis and silico-tuberculosis have been most troublesome. Other diagnoses to be considered are the other pneumoconioses, fungous infections, miliary carcinomatosis, and other forms of chemical pneumonitis.

TREATMENT

There is no effective treatment. According to DeNardi⁹ and associates, early diagnosis is imperative plus removal from any environment producing lung irritation. The patient should be restricted to minimal exertion and do his utmost to avoid acute infections. Residence in a dry and warm climate is conducive to clinical improvement.

PROGNOSIS

Gardner,⁶ who analyzed most of the cases seen by the various authors, described this disease as one of chronicity and high mortality. Pascucci,¹² who described 32 cases from the files of Dr. Gardner, recorded 30 per cent deaths, 30 per cent unimproved or slightly worse, and 40 per cent improved. In the community dealt with in the present report there were 11 known cases with three deaths. Of the eight survivors, five are chronically dis-

abled, two show clinical improvement and the course of one appears stationary. In the 36 cases described by Hardy,⁴ there were six deaths, seven showed a severe form of the disease, 14 were moderately severe, five were mild and four were asymptomatic.

TOXICOLOGY

The methods of analysis are both chemical and spectographic.¹³ Owing to the very small amount of beryllium found in the tissues, the chemical method has been abandoned in favor of the spectographic.

Several points must be made clear. At the present stage of our knowledge, the presence of beryllium in the tissues would indicate only that the individual had inhaled beryllium during life.¹⁴ This would tend to support a diagnosis of chronic berylliosis if warranted by the autopsy findings. There is no minimal level for beryllium that need be present in the tissues in order to make a diagnosis of pulmonary granulomatosis in beryllium workers.¹⁵ There is no recognized relationship between the amount of beryllium found in the tissues at autopsy and the pathologic state and there is no apparent relationship between the duration of the disease and the stage of pathologic change.

The amount of beryllium found at autopsy in the three cases was as follows:

	Lung	Liver	Kidneys	Lymph Node	Spleen
<i>Case 1</i>					
Lab. A	0.05 microgram/100 gm.				
Lab. B	nil or 0.00008 microgram/100 gm.				
<i>Case 2</i>					
Lab. A	0.07 to 0.08 microgram/100 gm.	Less than 0.05 microgram/100 gm.	*Less than 0.07 microgram/100 gm.		
Lab. B	0.93 microgram/100 gm.	1.48 micrograms/100 gm.		6.4 micrograms/100 gm.	0.17 microgram/100 gm.
<i>Case 3</i>					
Lab. B	0.237 microgram/100 gm.	Nothing or less than 0.008 microgram/100 gm.	Nothing or less than 0.02 microgram/100 gm.	0.665 microgram/100 gm.	Nothing or less than 0.02 microgram/100 gm.

The tissue on Case 1 was not sent in for analysis until some one and one-half years after the autopsy was done. Spectrographic analysis of the lung ash showed a reading of 5, which only indicated that there was beryllium in the lung.¹⁹ The histology was similar to that found in workers exposed to beryllium and it was considered a case of chronic berylliosis.

The tissues in Case 2 were sent to both laboratories at the same time soon after the autopsy was completed and analyzed by the spectrographic method. The varied results were merely an indication of the difficulty in spectrographic analysis at the present time.

In the cases on hand, the highest amounts were found in the lymph node first and the lung next. Martland⁷ obtained much higher values in two cases, up to 20 micrograms per 100 grams of lung. The largest amounts were found in bone. No bone was sent in for analysis in this series.

DeNardi and associates⁹ recovered beryllium from urine in two of four cases. These findings by themselves would only indicate exposure but along with typical clinical and roentgenographic findings would probably indicate disease.

No beryllium has been found in small numbers of control lungs and in several cases of Boeck's sarcoid. More work will have to be done before these findings take on any significance.

The public health aspect of the situation is obvious. Fumes and dusts from a beryllium plant should be properly disposed of and should not be permitted to pollute the air. The individual worker should exert great care. His work clothes and any of the containers which held beryllium or its products should never leave the factory, as there is suggestive evidence that these have been the source of exposure in several cases.

SUMMARY AND CONCLUSIONS

1. Three autopsied cases of chronic pulmonary granulomatosis occurring in residents near a beryllium plant are recorded.
2. Occupational histories on both worker and "neighbor" cases in this community are presented.
3. A low incidence, spotty distribution and lack of relationship of the severity of the disease to the degree of exposure, were characteristic.
4. The onset of the disease in the worker cases was delayed for periods of 27 months to four and one-half years after the last exposure.
5. Sputum studies and other laboratory examinations were essentially negative.
6. The history, clinical picture and roentgen-ray studies were fairly characteristic. Once the physician is aware of the disease, the diagnosis will be made with greater frequency.
7. The chief autopsy findings were confined to the lungs. The microscopic sections showed a diffuse replacement of the lung parenchyma by a nodular and diffuse granulomatous lesion. The focal areas were always

prominent. Granulomatous lesions were always present in the hilar lymph nodes and less frequently in the liver and spleen. The patients died of pulmonary insufficiency with right-sided heart failure.

8. Beryllium was recovered from the tissues in Cases 2 and 3. Spectrographic analysis of the lung ash in Case 1 revealed the presence of beryllium.

9. At the present stage of our knowledge, the recovery of beryllium in the tissues would only indicate that the individual had inhaled beryllium during life. This finding would tend to support a diagnosis of chronic berylliosis if warranted by the autopsy findings.

10. Beryllium analysis should be done on autopsy material from this area on individuals with no history of chronic pulmonary granulomatosis. This might help in a determination of the relationship between exposure, the finding of beryllium in the tissue, and disease.

Addendum: Since this article was accepted for publication, there have been two additional autopsied cases, both white females, aged 53 and 26 years respectively. No history of exposure was obtainable in the case of the 53-year-old female. The husband of the 26-year-old female worked in a beryllium plant for a period of eight weeks in December 1942, two years before the onset of symptoms in the patient and seven years before her death. She, however, denied ever cleaning his work clothes.

This brings the total series of autopsied neighborhood cases to five, all white females. The age range was seven to 53 years.

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BARBITURATE INTOXICATION: A CLINICAL ELECTROENCEPHALOGRAPHIC STUDY *

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IN the process of recording from a large number of patients admitted to this hospital in comatose states, it has been observed that individuals rendered unconscious by barbiturate drugs present a remarkably homogeneous EEG pattern. This pattern can be clearly differentiated from the recordings obtained in comatose states induced by all other agents and pathophysiologic mechanisms that have come under our observation.

The characteristic EEG pattern of barbiturate intoxication consists of a random frequency high voltage type. Slow waves occur in isolated and short sequences of sinusoidal 160 to 250 millisecond waves and in non-sinusoidal (or complex sinusoidal) slower discharges at around 300 milliseconds in duration. These latter waves often have higher frequency oscillations superimposed. The higher frequency waves occur in two main bands; the first ranges between 12 and 15 waves per second and the second ranges around 18 to 24 per second. The randomly admixed waveforms of relatively high voltage give the general pattern an irregular modulation.

The incidence of acute barbiturate poisoning has increased steadily in recent years. Hambouger¹ found that one of every 1900 hospital admissions was due to acute barbiturate poisoning. He reported a death rate of 7.3 per hundred. Where studies are restricted to severe intoxications (coma), the mortality rate may run as high as 15 per cent.² Recovery depends on rapid diagnosis and treatment.

In that there are no pathognomonic signs of barbiturate intoxication, the diagnosis is often difficult to establish in the absence of an adequate history. The clinical findings are similar to those of opium poisoning, uremia, and coma due to other causes. Clinical accounts in the literature vary and are at times contradictory, presumably because the authors are describing different stages of intoxication. In general, the picture is one of initial ataxia, confusion, and clouding of consciousness, then of deepening coma, with occasional periods of restlessness. There is an ever lessening response to all common modes of stimulation. The temperature is subnormal, but it may rise if an intercurrent pneumonitis develops. The pulse is slow but becomes rapid and thready as shock supervenes. The blood pressure is depressed but vasomotor collapse occurs only terminally. The respirations are shallow and slow. Cyanosis develops if the airways are obstructed. The pupils are usually constricted and react sluggishly to light. They may

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become fixed. Dilated pupils are sometimes seen as a very early or very late phenomenon. The corneal reflex disappears late. The tendon reflexes are depressed, as are the gag, coughing and swallowing reflexes. They may disappear completely in deepest narcosis. Vomiting may be present at any time, but this reflex also vanishes. Death, if it comes rapidly, is from respiratory failure. If life is prolonged several days, then death may follow from shock or pneumonia.³

At the present time a positive diagnosis can be made by finding barbiturates in the stomach washings, blood, urine, or organs at post mortem. Urinalysis is the method of choice. Koppányi and his associates perfected the cobalt color reaction by which any barbiturate can be detected in the urine following ingestion.^{4,5} This test is convenient, but it is not specific.⁶ False positives are obtained with acetates, sulfonamides, theophylline, and a number of other compounds.⁷ It is sometimes negative in the presence of clinically or experimentally demonstrated barbiturate intoxication. Kozelka⁸ and others have described a method for gravimetric isolation and identification of barbiturates in pure form. This determination can hardly be completed on the same day that the specimen is obtained; consequently, it is of little value to the treatment of the patient.

Because of the general difficulties encountered in the differential diagnosis of comatose states^{9,10} and the relative homogeneity of the recorded wave patterns in 11 patients, several representative sample tracings and case histories will be presented together with these data; and for contrast, some of the other common conditions productive of comatose states and their EEG concomitants will also be detailed.

CASE REPORTS

Case 1. On December 17, 1946 a 27-year-old woman took an unknown quantity of phenobarbital and was found unconscious at around midnight. Her husband noted a partly empty container of "sleep" pills on the patient's bed table. On admission to the hospital she could not be aroused. Her temperature was 98.6° F.; the blood pressure was 100/60 mm. Hg; the pulse was 88 per minute; the respirations were 18 per minute, deep and sonorous. Her pupils were pinpoint. The extremities were flaccid. Between midnight and noon of the following day she received a total of 75 mg. of picrotoxin in doses of 4.5 to 6 mg. each and a total of 2 grams of caffeine sodium benzoate in 0.5 mg. doses; she was given intravenous 10 per cent glucose in water and oxygen inhalations when she became cyanotic. Despite treatment little change in her general condition was observed and the diagnosis of barbiturate intoxication as the sole agent for the unresolved coma came into question.

At 1:00 p.m. on December 18, 1946, an EEG was done. At that time her temperature was 100° F., her blood pressure 105/60; her pulse rate 100 per minute; respirations were 20 per minute, deep and regular. The pupils were still pinpoint, but reacted minimally to light. The eyeballs were fixed in forward gaze; no corneal reflexes could be obtained. Pharyngeal reflexes were obtained when aspiration was attempted; sporadic vomiting occurred. There was no response to auditory stimuli and only minimal withdrawal to very noxious stimuli. Essentially no spontaneous movements of the extremities were noted. Tendon reflexes were equal and active. She was incontinent of urine. Following the EEG, treatment was reinstituted. She

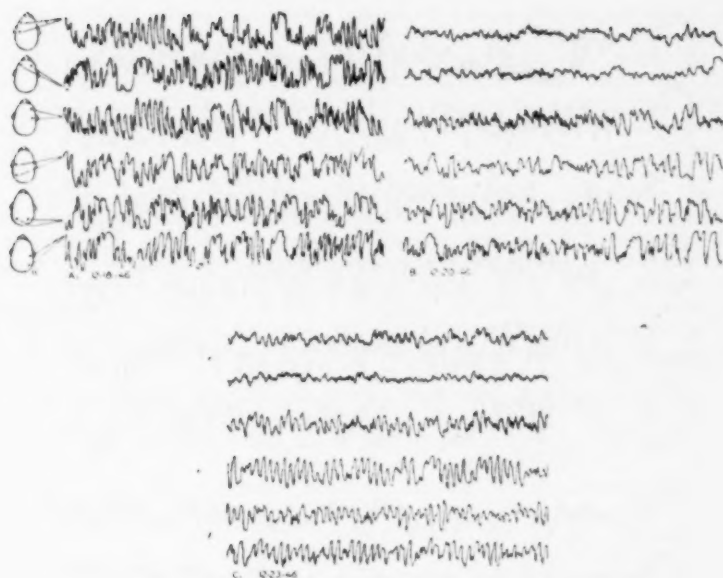


FIG. 1.

A. 12-18-46

Attitude and condition of patient: Comatose.

Fundamental frequency: random fast and slow activity is interspersed with short runs of alpha frequency waves.

SLOW WAVES: isolated and short sequences of 166 millisecond waves are seen in all leads. Throughout, isolated complex sinusoidal waves of 200 to 300 millisecond duration are observed.

Fast waves: a 12 to 14 per second band and an approximately 18 per second rhythm are prominently dispersed throughout the tracing.

Amplitude characteristics: high voltage; irregular modulation.

Additional features: the alpha and lower frequency sequences are characteristically of short duration throughout the recording, irrespective of the several combinations employed.

B. 12-20-46

Attitude and condition of patient: coöperative, but tired.

The voltage output is reduced. Only isolated and short runs of 166 to 200 millisecond waves are observed. The complex sinusoidal waves are no longer prominent. Fast activity, of low amplitude, ranges between 20 to 24 waves per second.

C. 12-23-46

Attitude and condition of patient: Alert, coöperative.

A 9 per second rhythm dominates the tracing. Only random high frequency activity is seen. Transient, isolated 150 millisecond waves are seen in all leads.

received an additional 40.5 mg. of picrotoxin and another gram of caffeine sodium benzoate in divided doses, plus CO₂ inhalations and penicillin. At around 10:00 p.m. on December 18, some spontaneous movements of the head and limbs and corneal reflexes were observed. By 6:00 a.m. on December 19 she "sleepily" responded to questions and at 8:00 a.m. was able to talk coherently and to take fluids by mouth. On December 25 she was discharged from medical treatment.

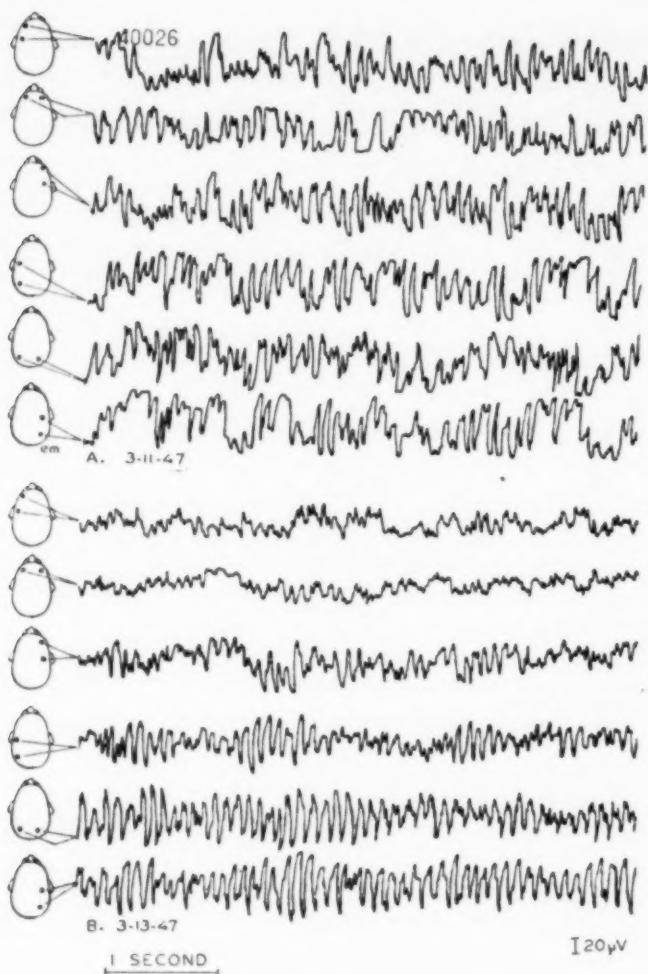


FIG. 2.

A. 3-11-47

Attitude and condition of patient: Comatose.

Fundamental frequency: is random, only isolated alpha frequency waves are observed.

SLOW WAVES: isolated, but prominent, 166 to 200 millisecond waves are seen in all leads. Complex sinusoidal waves (sharp or choppy waves) of longer duration are also prominent.

Fast waves: 12 to 14 per second and 18 to 22 per second waves are dominantly interspersed between the lower frequency oscillations.

Amplitude characteristics: high voltage; irregular modulation.

Additional features: the non-sinusoidal slow waves have much higher frequency activity superimposed; this gives the baseline a choppy character.

Case 2. A 53-year-old veterinarian was admitted to the hospital at 4:00 p.m. on March 11, 1947. He had been observed apparently well at 1:30 p.m., but at 2:00 o'clock he was found comatose. No relevant history was obtained except that no drugs had been found in his vicinity. On hospitalization he was in deep coma. The blood pressure was 135/80; pulse rate was 84 per minute; respirations were 28 per minute and labored; temperature was 98.6° F. His lips and mucous membrane of the buccal cavity were cyanotic. He responded neither to painful nor auditory stimuli. Eyeballs were fixed in forward gaze. Pupils were constricted, but reacted slowly to light. Superficial reflexes were absent. His limbs, at first flaccid, gradually became rigid. Deep tendon reflexes were absent at the left knee and ankle joints, but active on the right side. An EEG was performed just after admission to the hospital. At that time no clinical neurological localizing signs were observed. Lumbar puncture was then performed and a pressure of 150 mm. of water was noted. Almost immediately after the lumbar puncture, at 5:45 p.m., he regained consciousness, but he then lapsed into somnolence. On the following morning, he was apparently well. Although the diagnosis of barbiturate intoxication was suggested to the medical service, for some unknown reason the full significance of the findings was not appreciated and the patient was treated medically as a latent hypertensive. On April 7 he was discharged from medical treatment.

He was readmitted to the hospital on July 6, 1947 at 10:00 p.m. in coma. He had been found unconscious at 6:00 p.m. Temperature was 99.7° F., pulse 70 per minute, respirations 22 per minute, blood pressure 110/76. No spontaneous motor action was present. He could not be aroused by painful or auditory stimuli. Eyes were fixed in forward gaze. Pupils were constricted and did not react to light. Corneal reflexes were absent. The gag reflex was present. His deep tendon reflexes were diminished, but more on the right side. The abdominal reflexes were absent. He had bilateral plantar extensor responses. The clinical impression was of cerebral thrombosis. He was given supportive treatment again but his condition persisted through the night with little change. At 9:00 a.m. spontaneous movements of the extremities were observed. Corneal and pupillary reflexes were present but sluggish. Tendon reflexes were diminished but the Babinski signs were no longer elicited. He responded somewhat to painful stimuli.

An EEG was performed at 11:30 a.m. This time the diagnosis was clearly and definitely established, and specific treatment (picrotoxin) was instituted. Urinalysis confirmed the EEG diagnosis. On the following morning, he was alert and rational. He reluctantly admitted that he had been taking nembutal for three years to combat depression and anxiety and that his hospital admissions were a result of nembutal overdosage with suicidal intent.

Case 3. The patient could not be aroused on the morning of May 24, 1948, despite strenuous efforts of his mates. A box of seconal tablets was found on his person. An EEG test was obtained immediately after hospitalization. On examination the patient showed mild cyanosis and markedly reduced responses to tendon stretch reflexes! Respirations were 16 per minute; pulse ranged around 78 per minute; and the blood pressure was within normal limits. Bogan's test was negative, but the urine was positive for barbiturates (19 mg./100 c.c.). After administration of caffeine and sodium benzoate intramuscularly, he could be aroused, but his speech was incoherent. He staggered when attempting to walk. He was able to state that he had taken 7

B. 3-13-47

Attitude and condition of patient: Alert, cooperative.

An approximately 10 per second rhythm dominates the record. No slow activity of definite brain origin is recognized.

Random fast waves are observed, but are more prominent in rostral derivations. Only occasional 18 per second waves are seen in the parietal and occipital regions.

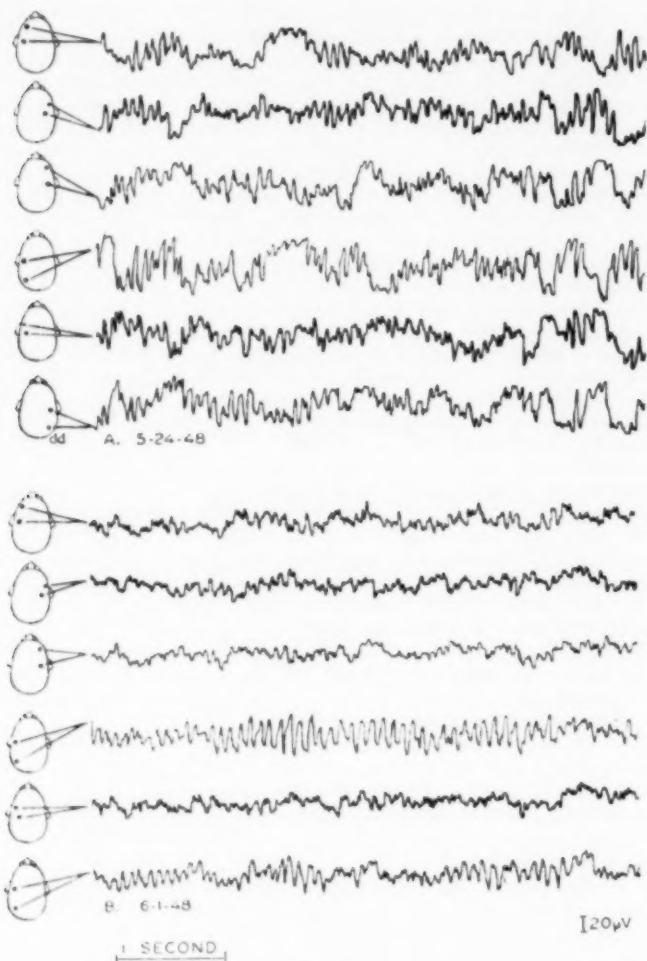


FIG. 3.

A. 5-24-48

Attitude and condition of patient: Comatose.

Fundamental frequency: is random, only very short runs of 10 per second activity are recognized.

SLOW WAVES: isolated, 160 to 200 millisecond waves are seen in all leads. Even slower activity of complex sinusoidal form is observed in a general distribution.

Fast waves: 12 to 16 per second sequences and approximately 20 per second activity are the dominant characteristics of this record.

Amplitude characteristics: average to high voltage; irregular modulation.

Additional features: at times the very slow activity takes on the character of baseline swinging.

second capsules and one luminal capsule. About 24 hours after taking the sedative, he was able to tell of the events of the previous evening. He had been on a date and had a quarrel with his girl friend. This, combined with the fact that he was homesick for his family in California, led to his suicidal attempt.

Case 4. A 21-year-old man suffered a severe head injury without fracture in April 1946. This was complicated a month later by a subdural hematoma and brain abscess. An EEG was recorded on May 13. Craniotomies were performed May 21 and June 28, respectively, to evacuate the hemorrhage and abscess. He made an uneventful recovery.

On August 21, 1946 he was observed to be drowsy; his speech was mumbling and incoherent. He appeared to understand what was said to him. He was restless, and kept trying to get out of bed. Urinalysis revealed no evidence of barbiturates. An EEG was performed the same day, at which time the patient was completely unaware of his environment and could not be aroused by usual auditory stimuli. On the basis of the EEG findings he was treated with benzedrine and intravenous fluids, and on the next day he regained consciousness. Subsequent history revealed that he had taken an overdose of phenobarbital in a suicidal attempt.

On March 10, 1947 he was found in a bus terminal in a very drowsy state. He was taken to a civilian hospital. Here he was observed to be disoriented and transiently stuporous. He was incontinent of urine and he exhibited carpopedal spasm. During the night his stupor deepened into coma. His blood pressure rose from 118/68 to 140/90; his respirations were 28 per minute; the pulse was 120 per minute. His pupils became constricted, he did not respond to painful stimuli; and the knee-jerks, ankle-jerks and abdominal reflexes were no longer elicited.

On the following day he was transferred to the U. S. Naval Hospital, Bethesda, Md. On admission his pulse was 100 per minute; respirations 24 per minute; blood pressure 142/106; the temperature was 99° F. The pupils reacted to light; corneal reflexes were present; abdominal and deep tendon reflexes of the lower extremities were not elicitable.

Between 12 p.m. and 1:00 a.m. on the day of admission, he was given 18 mg. of picrotoxin in three doses of 6 mg., and 1.0 gm. of caffeine sodium benzoate in two 0.5 gm. doses. When the EEG was performed on March 12 at 9:00 o'clock, the patient was still comatose. His breathing was stertorous and he required frequent aspirations. He was completely unresponsive and moved only occasionally. Later in the morning he was responsive to strong stimuli. On March 13 he awakened occasionally, took oral fluids, and frequently talked freely. On March 19 he had completely recovered. It was then established that he had taken an "overdose" of sodium dilantin while under the influence of ethyl alcohol.

On April 8, 1947 he obtained and ingested 70 quarter grain tablets of phenobarbital. About 11:30 a.m. he was observed to be unsteady and confused. At 11:45 a.m. he was unconscious. He was lavaged, given 6 mg. of picrotoxin at 12:10, 12 mg. at 12:20 and 15 mg. at 1:10. He responded to painful stimuli. At 2:10 p.m. he was able to drink some coffee. At 3:00 o'clock an EEG was performed. At this time he was again comatose. His pulse was 80 per minute; his respirations 18 per minute. Later he was able to walk when supported, but at 7:00 p.m. he again lapsed into coma and was given 6 mg. of picrotoxin. His corneal reflexes were no longer active at this time. At 11:20 he was given more picrotoxin. Following this he improved slowly and had recovered by April 11.

B. 6-1-48

Attitude and condition of patient: Alert, coöperative.

The fundamental frequency ranges between 10.5 to 13 waves per second, with the alpha activity more prominent over the left cerebral hemisphere.

No slow waves are observed.

Fast activity is random.

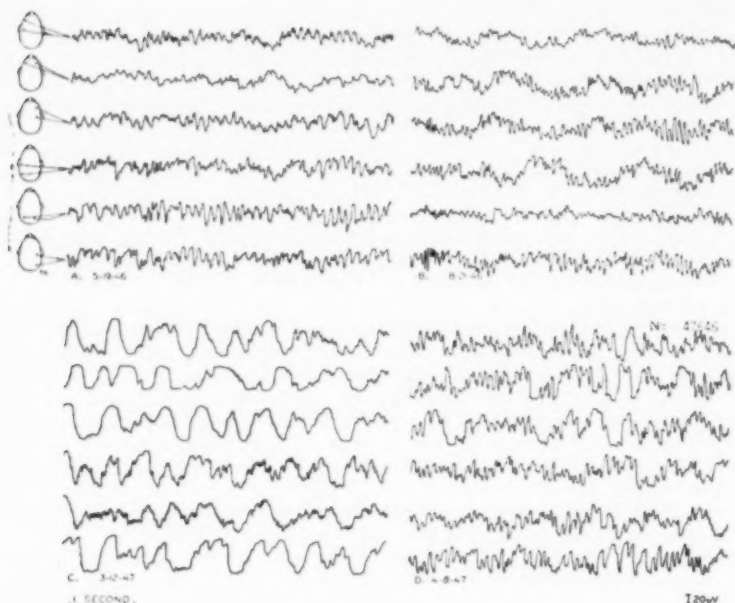


FIG. 4.

A. 5-19-46

Control

Attitude and condition of patient: Alert, coöperative. 7.5 gr. of sodium amytal 36 hours prior to test.

Fundamental frequency: consists of a poorly sustained 8 per second rhythm.

SLOW WAVES: none of definite brain origin.

Fast waves: of random frequency are increased in amount (general).

Amplitude characteristics: average voltage; not well modulated.

B. 8-21-46

Attitude and condition of patient: Unresponsive to auditory stimuli, but restless. Mild barbiturate intoxication.

Fundamental frequency: is fast; sequences of 12 per second waves are prominent.

SLOW WAVES: choppiness of the baseline gives the tracing a slow characteristic.

Fast waves: 18 to 24 per second activity is prominent in all leads.

Amplitude characteristics: average voltage; irregular modulation.

C. 3-12-47

Attitude and condition of patient: Comatose. Ethyl alcohol intoxication.

Fundamental frequency: slow.

SLOW WAVES: 1.5 to 2 per second waves dominate the tracing. This slow activity is more clearly defined over the right cerebral hemisphere.

Fast waves: except for some muscle potentials are not prominent.

Amplitude characteristics: average to high voltage; irregular modulation.

D. 4-8-47

Attitude and condition of patient: Comatose. Barbiturate intoxication.

Fundamental frequency: is random; only short sequences of approximately 10 per second waves are observed.

SLOW WAVES: isolated, but prominent, 166 to 250 millisecond waves are seen in a general distribution.

Fast waves: between 12 and 15 per second and around 20 per second are prominently superimposed on, and interspersed between the slower oscillations.

Amplitude characteristics: average to high voltage; irregular modulation.

Case 5. A 25-year-old man was discovered in coma at 5:45 p.m. on September 30, 1947, and was brought to the sick bay when he could not be aroused. His temperature was 98.6° F.; his pulse 100 per minute; respirations 22 per minute; the blood pressure 130/80. His pupils were constricted, equal and reacted to light. After an hour he recovered spontaneously and was able to respond to questioning, but he was moderately confused.

It was suspected by the admitting officer that the patient was recovering from an epileptic convulsion. The following morning an EEG was obtained. He ap-

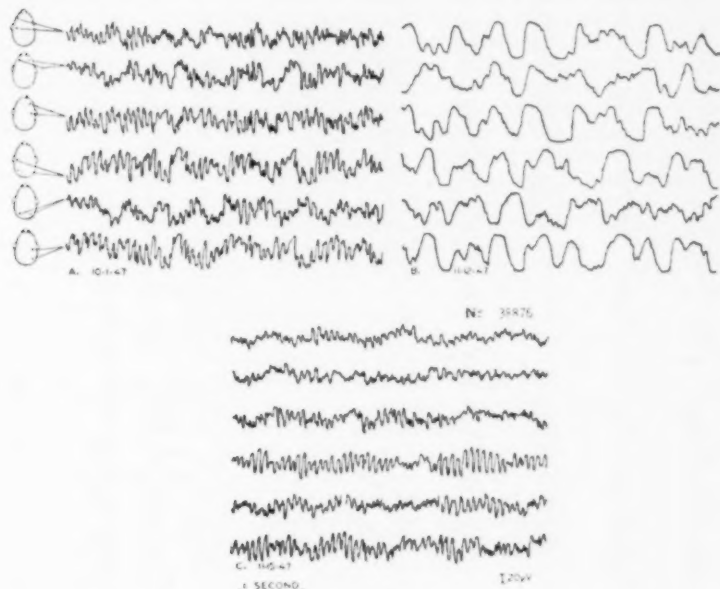


FIG. 5.

A. 10-1-47

Attitude and condition of patient: Drowsy; retarded responses to all auditory stimuli. (Barbiturate intoxication.)

Fundamental frequency: is random, but short sequences of 9 to 10 per second activity are prominent.

SLOW WAVES: non-sinusoidal (choppy) 250 to 300 millisecond waves are seen in all leads.

Fast waves: 11 to 15 per second and approximately 20 per second activity are prominent (general distribution).

Amplitude characteristics: high voltage; irregular modulation.

B. 11-12-47

Attitude and condition of patient: Comatose. Ethyl alcohol intoxication.

One and one-half to three per second activity dominates the tracing. Almost no fast activity is observed. The voltage throughout is high; it is poorly modulated.

C. 11-15-47

Attitude and condition of patient: Alert, cooperative.

A 9.5 to 10 per second alpha rhythm dominates the tracing. Random fast activity is increased in amount and general in distribution. No slow waves of brain origin are recognized.

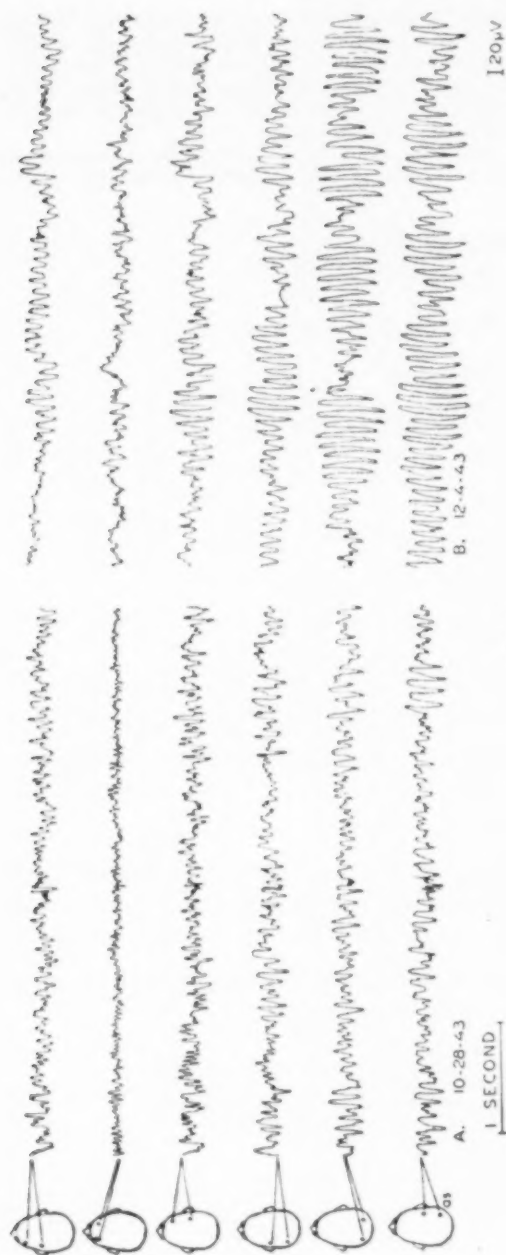


FIG. 6.

A. 10-28-43

Attitude and condition of patient: Increased, indiscriminate language output.

Fundamental frequency: is not well defined—only short runs of 8 to 9 per second waves are observed.

SLOW WAVES: none of brain origin.

Fast waves: 12 to 15 per second and 20 to 22 per second waves are prominent in all leads.

Amplitude characteristics: low to average voltage; not well modulated.

B. 12-4-43

Attitude and condition of patient: Alert, cooperative.

An average to high voltage, well regulated, 10.5 per second rhythm dominates the record. Fast activity is not prominent. No slow waves are observed.

peared fatigued and drowsy. It was the examiner's impression that the tracing was more consistent with barbiturate intoxication than with the epilepsies. Some time later the patient admitted that at approximately 4:30 p.m. he had taken an indeterminate quantity of barbiturates (Elixir-of-phenobarbital) in an attempt to ward off some of his anxieties.

He returned to duty October 3, 1947. On November 12, at 1:15 p.m., he was again admitted to the hospital in coma. He had been observed at 12:30 walking with a staggering gait. He appeared sleepy. It was noted at the time that the patient did not return a salutation to a superior. He was later found unconscious with a broken bottle of elixir of terpin hydrate lying beside him. An odor resembling ethyl alcohol was on his breath. His pupils were equal, but constricted, and they reacted sluggishly to light. Slight rotary motion of both eyes was observed. A cerebral spinal fluid Bogan's of 3.0 mg. per cent was reported and he was given insulin and hypertonic glucose infusions intravenously. At 4:30 he was able to respond in a sleepy, inappropriate manner to questions. An EEG was done at this time. By 8:30 p.m. his responses were coherent and relevant. He admitted he had taken between five to eight ounces of elixir terpin hydrate and codeine to "quiet his nerves." He recovered uneventfully.

Case 6. On the day prior to hospitalization, this 30-year-old woman sustained a head injury upon striking her head on a change box in a moving streetcar. Immediately following the accident, she felt well enough to proceed to work. While working she lost consciousness. She was then transferred to the U. S. Naval Hospital, Bethesda, Md. for observation and study. On admission to the hospital the patient was alert and did not appear acutely ill. She had a remarkable propensity to excessive verbalization, but despite the intense quantity of output, all speech was fairly appropriate. She complained of transient double vision. On examination only incoördination of fine movements of the hands and lateral nystagmus were observed. At this time the patient was entirely amnesic for all events of the past 24 hours. She stated that within the past few weeks she had received the news of the deaths of her brother and fiancé. Following this news she indulged in great activity in order to "keep from thinking." Associated with this incessant drive to keep going, she became unable to sleep. Often she required only one or two hours of sleep to keep her "going" for days. Feeling that she should sleep more, she took recourse to phenobarbital. She remembers taking "two pills" on the evening preceding the streetcar accident.

Case 7. The patient was a 59-year-old man who was admitted to this hospital on June 3, 1948 complaining of pain in the chest and left shoulder, shortness of breath and hemoptysis. He had had two previous admissions. From June to September 1947, he was under treatment for asthma on a cardiac basis. The second admission was in February 1948 for a severe, radiating pain in the chest and left arm. Following the second period of treatment he had been able to carry out his duties as night watchman until two days before the final hospitalization. On this admission, he appeared chronically ill. Blood pressure was 200/105; the heart was enlarged, but no murmurs were heard. Blood urea nitrogen was 86.5 mg./100 c.c. on June 4. The red cell count of the same day was 2,400,000; hemoglobin 52 gm. (7.5). He voided frequently. On June 7 the patient had a generalized convulsion of five to seven minutes' duration. He showed pallor, labored breathing and slow, regular pulse, but responded to therapy. Following this episode he remained semicomatose. When "awake" he responded only to painful stimuli and loud noises. Blood urea nitrogen was increased to 225 mg./100 c.c. of blood at this time. The next day he was still comatose and unable to void. One hundred c.c. of urine were removed by catheter. Death occurred on June 10.

Case 8. This 52-year-old patient was admitted to the hospital on May 21, 1948 in a comatose condition, suffering from multiple head injuries as the result of being struck by a taxicab. He had received previous emergency treatment, during which period he vomited twice.

On examination the following day the upper and lower limbs were observed in strong, symmetrical extension. Full head rotation to either side failed to alter the extreme hypertonicity of the limb muscles. The deep tendon reflexes were active and essentially equal. Positive Hoffmann and Babinski signs were elicited on the left side. The right pupil was larger than the left, neither reacted to light. The eyes were maintained in forward gaze. The left eye contained a large, sub-hyaloid hemorrhage. No papilledema was recognized. Strong pressure elicited no evidence of pain perception. Lumbar puncture showed an initial pressure of 296 mm. of water. The fluid contained dark red blood. Following bilateral trephination in the temporal region, the patient did poorly and died on May 31.

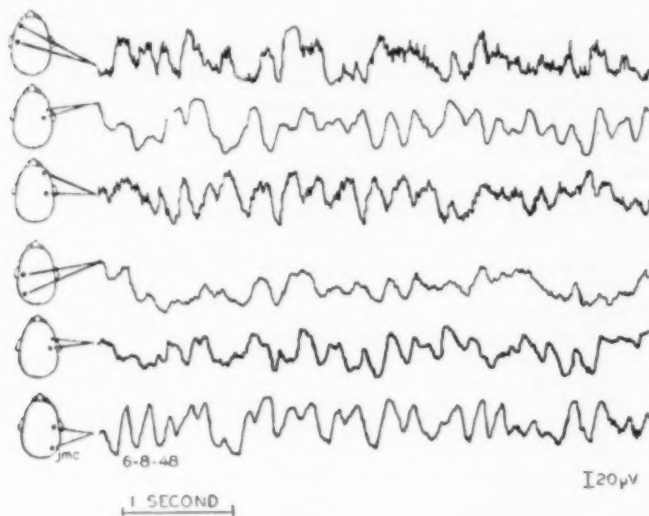


FIG. 7.

A. 6-8-48

Attitude and condition of patient: Comatose.

Fundamental frequency: is slow.

SLOW WAVES: around 4 per second, completely dominate the record.

Fast waves: of muscle origin are superimposed on the frontal output.

Amplitude characteristics: average to high voltage; poor modulation.

At autopsy, multiple various sized intracerebral hemorrhages—all of the same age—were observed. They were most prominent in each frontal and in the left temporal regions. One hemorrhage had ruptured into the third ventricle. Subarachnoid hemorrhage was also observed.

Case 9. At 3:30 in the morning of February 3, 1948, this patient, a 67-year-old man, was found on the floor leaning against the door of his bathroom. He was unable to use his left arm and left leg; he appeared only partially aware of his surroundings. On admission to the hospital six hours later, he complained of severe pain

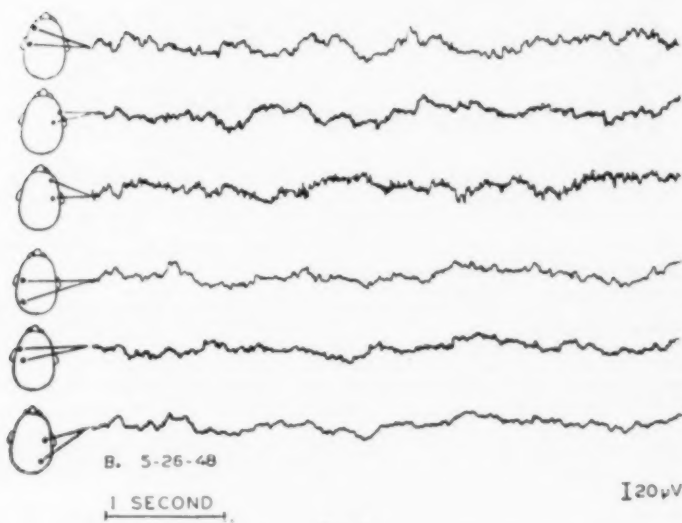
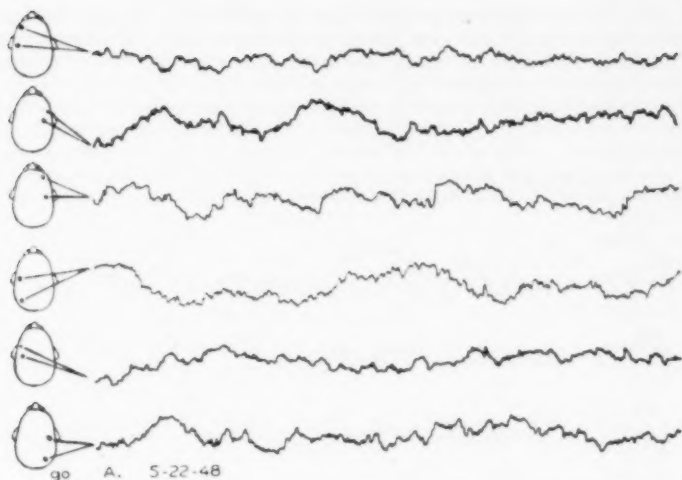


FIG. 8.

A. 5-22-48

Attitude and condition of patient: Comatose.

Fundamental frequency: is random.

SLOW WAVES: very low amplitude 166 to 200 millisecond waves are seen in all leads.

Fast waves: of random frequency dominate the tracing.

Amplitude characteristics: low voltage.

B. 5-26-48

The basic pattern of the earlier tracing persists.

in the right side of the head, particularly in the frontal region. He responded poorly to questioning. There was a left homonymous hemianopsia. Routine laboratory tests, including spinal fluid pressure, were within the range of normal. The patient was very restless, and incontinent of urine and feces.

On the afternoon of February 5, he became more drowsy and the spinal fluid pressure was elevated to 290 mm. of water. A ventriculogram performed shortly afterwards showed a shift of the left lateral ventricle to the left. Craniotomy was done. An apparently malignant, firm mass deep in the right anterior temporal region was partially removed. The patient was unable to talk on the following day, but

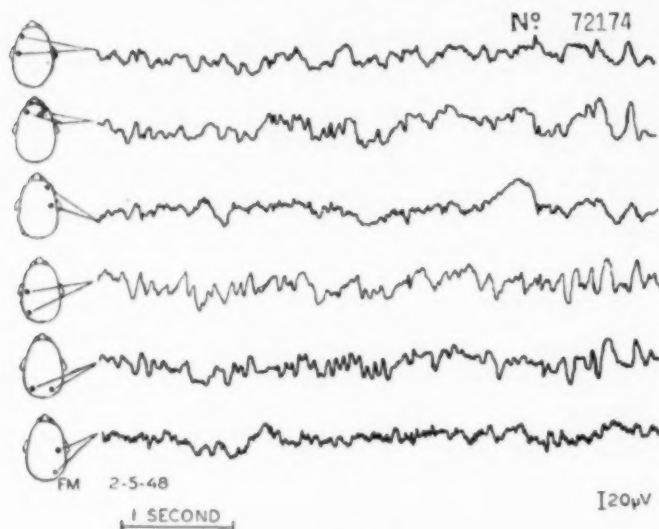


FIG. 9.

A. 2-5-48

Attitude and condition of patient: Transient coma.

Fundamental frequency: is random.

SLOW WAVES: 166 to 200 millisecond waves are moderately prominent over the left cerebral hemisphere.

Fast waves: of random frequency are recognized in all leads.

Amplitude characteristics: low to average voltage; irregular modulation.

Additional features: The electric output over the right brain is definitely decreased when compared with the left.

could carry out simple commands. On February 7 he failed to respond to any requests. Numerous spinal taps continued to show elevated pressure. The patient died on February 8.

At autopsy a massive hemorrhagic infarct was recognized to involve the entire right cerebral hemisphere. In a detailed study no neoplastic tissue was recognized.

Case 10. This patient was admitted to the hospital on June 27, 1948 in a comatose state. Two days previously he had suddenly fallen and was unable to talk or move. The family physician made a diagnosis of "clot on the brain." On examination the temperature was 102.6° F., his pulse 72 per minute, and the blood pressure 150/80. He responded by a slow withdrawal movement to painful stimuli. The

pupils were constricted but reacted to light. The eyes were maintained in conjugate forward gaze. No ptosis was evident. There was little "spontaneous" movement. The extremities of the right side were flaccid, but the deep tendon reflexes were slightly increased as compared with the left. The Babinski sign was positive on the right. Repeated blood sugars ranged between 267 and 300 milligrams per 100 c.c.

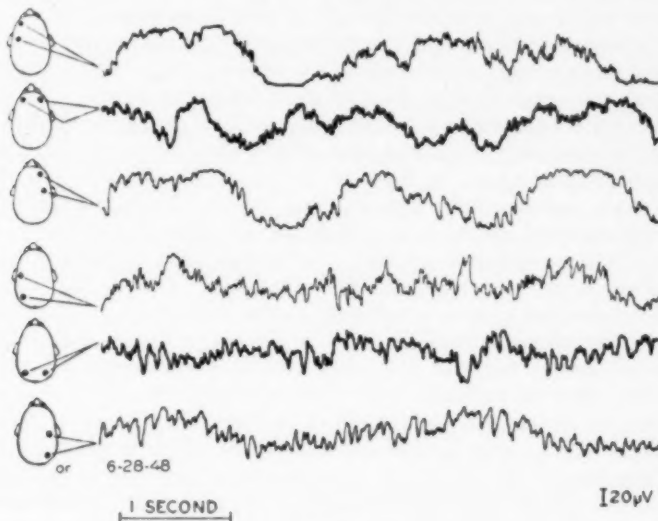


FIG. 10.

A. 6-28-48

Attitude and condition of patient: Transiently comatose. Unresponsive during the intervals of "awareness."

Fundamental frequency: is random; some approximately 8 to 9 per second activity is observed in all leads.

SLOW WAVES: isolated 150 millisecond waves are recognized in general distribution.

Fast waves: of random frequency and of muscle origin are superimposed on the basic oscillations.

Amplitude characteristics: average voltage; irregular modulation.

Additional features: Baseline swinging (sweat artefact) is prominent in the frontal derivation.

of blood. The CO_2 combining power was noted on two occasions as 40 volumes per cent. The urine showed 3 to 4 plus sugar. Acetone was reported positive in one urine specimen. He was treated with insulin, digitalis, and penicillin. His course was downward and he died the day following hospitalization. Autopsy was not performed.

DISCUSSION

Since 1943, a series of patients admitted to this hospital in barbiturate induced coma has been studied. The diagnosis in each case has been verified by a reliable history. In some cases the urine examination has been confirmatory. In two cases the diagnosis was established by the EEG despite negative urinalysis and was later confirmed by the history. All cases, to

date, of barbiturate induced coma have shown the characteristic pattern observed in the sample EEG tracings. In no comatose state resulting from other toxic agents has a similar EEG pattern manifested itself. It is of interest that, despite "specific" treatment in several cases, the electric output was entirely similar to that observed in other patients who had had no treatment whatsoever up to the time of the EEG examination.

Experimentally in man, the introduction of sodium amytal or sodium pentothal intravenously early results in a relatively high voltage, high frequency electric output ranging from 18 to 24 waves per second.^{11, 12} As the administered dose is increased, this relatively high frequency oscillation is replaced by essentially sinusoidal slow activity ranging from 2 to 6 waves per second, depending on the depth of coma attained. In quite deep barbiturate coma, *experimentally induced*, slow activity dominates the tracing. These experimental results consequently are not precisely similar to those observed in the cases herein reported. The difference is not easily accounted for—although the relatively slow rate of absorption of the barbiturates from the gastrointestinal system in contrast to the rapid passage of the intravenously administered drug, may well be the critical factor responsible for the combination of fast and slow wave activity in our series of cases even when deep coma, as clinically determined, was manifest.

From our results, the observation of *rhythmic* fast activity in the EEG of a patient who presents a clouded consciousness almost immediately points away from brain injury or other gross insults to the brain as the primary cause of the patient's difficulty (figure 6). Random fast activity, with or without slow baseline swing, in a comatose patient may point, however, as in figure 8, to massive structural lesions of the brain. It should be emphasized that the tracings in coma resulting from severe brain injury often do not take the form shown in figure 8. In certain cases, slow activity equal in amount to that seen in figure 5B dominates the tracing. In coma resulting from the presence of expanding intracranial neoplasms, the EEG pattern is ordinarily characterized by intense slow wave output. Hypoglycemic shock and diabetic coma are usually associated with high voltage slow activity.^{13, 14} Diabetic coma may, however, show a pattern similar to that observed in figure 10.

The co-existence of generalized fast and slow electric activity in tracings raises the question as to whether all of the derived potentials originate locally in the cortical neurones. Certain experimental evidence indicates that subcortical, probably thalamic cell masses, may be responsible for at least triggering of some of the relatively higher frequency oscillations, particularly in the 12 to 15 per second band.¹⁵ Whether the 18 to 24 per second high frequency band is determined by, or can be correlated with, thalamic or other subcortical functional activity has not yet been demonstrated. Recently data have been presented that suggest that the *slow* activity derived from the brain is a locally generated cortical process.¹⁶ This is arrived at by

the congruity of the simultaneous discharges from homologous regions of the brain and from the configuration of the wave contours.

CONCLUSIONS

1. Coma induced by barbiturate action gives rise to a characteristic EEG pattern.

2. This pattern is characterized by the co-existence of a slow wave output with two relatively high frequency bands. The slow activity occurs in isolated and short sequences of 160 to 250 millisecond duration waves. These latter waves often are of complex sinusoidal form. Superimposed and interspersed between this slow potential variation, higher frequency waves, 12 to 15 per second and 18 to 24 per second, of relatively high voltage are observed. The fast activity shows no grossly asymmetric wave forms. The random appearance of fast and slow activity gives rise to an irregular amplitude modulation.

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MUMPS ORCHITIS AND TESTICULAR ATROPHY. I. OCCURRENCE *

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MUMPS is the fourth most commonly reported communicable disease in the United States, being exceeded in frequency of occurrence only by measles, influenza, and chickenpox. During the five year period from 1942 through 1946 there were 1,015,796 cases of mumps reported, an average of over 200,000 cases per year.¹¹

It is estimated that 10 to 20 per cent of children in rural and 80 per cent in urban communities contract the disease before the age of 15 years.¹² Of all reported cases of mumps in Massachusetts from 1916 to 1937, 88.6 per cent occurred in children under 15 years, and the commonest age of attack was six years.⁹

Mumps is accepted as one of the ordinary childhood diseases to be expected sooner or later in the majority of children. Usually the disease, unlike some of the other virus infections, gives no cause for alarm; complications are rare, especially in children, and the over-all mortality is exceedingly low—only 0.12 per 100,000 in the Massachusetts study.

Among adults the most common complication of mumps is the orchitis occurring in males. Testicular involvement occurring in mumps was first marked by Hippocrates.¹⁸ The incidence of orchitis varies with epidemics and different authors. Wesselhoeft¹⁹ cited epidemics of varying size in which orchitis ranged from 3 to 100 per cent in incidence. Candel⁴ in interviewing 2368 Navy trainees found a history of mumps in 47.3 per cent with 17.6 per cent reporting simultaneous orchitis. The following series (table 1) was collected from the literature.^{1, 7, 12, 17, 19}

Orchitis rarely occurs in children contracting mumps before the age of puberty. Stengel¹⁷ was able, however, to find five cases of orchitis due to mumps occurring prior to the twelfth year. The disease has also been reported to attack the undescended testis of cryptorchids in whom this organ often retains its prepuberal character.¹⁹

Most authors now regard the orchitis to be the result of localization of the virus from the blood stream in the testis. The inflammation of the testis usually begins on the third to sixth day after onset of the parotitis and lasts five to 10 days. The orchitis may actually precede the parotitis or may not develop until as long as 44 days after the parotitis,¹⁰ and there have been a number of reports in which orchitis was the sole manifestation of mumps.^{3, 6, 19}

After the acute phase of the orchitis, the testis gradually decreases in size,

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This study was made while the writer was on active duty with the United States Navy. National Institutes of Health Postdoctorate Research Fellow, Department of Medicine, New York Hospital—Cornell Medical Center.

although in some cases it may remain swollen slightly for periods up to a year. The testis may return to normal size and consistency, or it may become softer and shrink beyond its normal size.

Atrophy of the testicular tissue following mumps orchitis is believed to be due both to the action of the virus upon the seminiferous tubules,¹⁸ and to the pressure of exudate and edema upon the tubules within the taut tunica albuginea.^{17, 19} The degree of atrophy is not necessarily proportional to the severity of the orchitis, and it does not affect all the tubules uniformly. In fact, Candel reports three instances of otherwise unexplained testicular atrophy which followed mumps parotitis in which there were no signs of clinical orchitis. Atrophy is usually perceptible within one to six months after the orchitis subsides.

TABLE I
Incidence of Orchitis in Various Epidemics of Mumps in Males

Author	No. of Cases of Mumps	Incidence of Orchitis
Catrin	10,601	18.5%
Wesselhoeft	8,153	18.0
Benard	5,000	15.0
Radin	4,397	13.9
Benard	2,000	20.0
Longuet	1,555	25.0
McGuinness and Gall	1,364	36.2
Brooks	1,059	24.0
Bailey and Haerem	551	19.0
Gellis et al.	502	32.0
Worden	250	16.4
Rambar	249	24.5
Dermon and Le Hew	126	35.0
Potter and Bronstein	112	11.6
Bangs	74	66.0

In the genital tract, mumps need not confine itself to the testes, but it may attack the epididymis, the spermatic cord and the prostate causing subsequent atrophy of these structures.^{12, 14, 19}

Mumps orchitis is more likely to be unilateral than bilateral. Stengel states that the testes are equally and unilaterally involved two to three times as often as they are bilaterally affected, and that there is no relation between the side of the parotitis and the side on which the orchitis develops. Wesselhoeft found the right testicle to be involved more often in unilateral orchitis. Reports from the literature concerning the frequency of bilateral orchitis are given in table 2.^{5, 10, 12, 17, 19}

TABLE II
Incidence of Bilateral Testicular Involvement in Mumps Orchitis

Author	No. of Cases of Mumps Orchitis	Incidence of Bilateral Orchitis
Catrin	1,961	30%
Wesselhoeft	1,208	16
Radin	554	18
Macleod		28
Laveran		30
Dermon and Le Hew	44	30

Wesselhoeft states, "Any change in the consistency of the testicle which can be determined any time after six weeks from the acute stage . . . should be termed atrophy," and he gave the incidence of atrophy to be 54.7 per cent among 347 cases of mumps orchitis. Reports from the literature concerning the frequency of post-orchitis atrophy are given in table 3.^{4, 6, 20}

The atrophy following mumps is usually asymptomatic. Occasionally there may persist a dull, neuralgic pain in the affected testis. Rare cases exhibiting loss of libido and signs of feminism have been mentioned.^{17, 19} There seems to be little danger of tumor formation in a testis atrophied as a result of preceding mumps orchitis, for only 0.5 per cent of 5,500 cases of testicular tumor reviewed by Gilbert⁸ had a history of mumps orchitis and atrophy.

TABLE III
Incidence of Testicular Atrophy Following Mumps Orchitis

Author	No. of Cases of Mumps Orchitis	Incidence of Atrophy
Wesselhoeft	347	55%
Candel	49	55
Dermom and Le Hew	44	48

Reports of the occurrence of sterility following mumps orchitis are sparse. Benard² found only one case of sterility among 175,000 cases of mumps in the French army. Stengel found two cases of sterility unquestionably due to mumps. Wesselhoeft states that prostatic atrophy is far more likely to bring about sterility than orchitis. Seguy,¹⁶ on the other hand, reported that 4 per cent of all cases of male sterility can be traced to mumps orchitis occurring after the age of puberty.¹⁸

It was the purpose of this study to investigate the incidence of occurrence of mumps orchitis and testicular atrophy in a large male population and to determine to what extent this affliction may impair the normal fertility of males contracting the disease.

MATERIALS AND METHOD

In order to determine the frequency of occurrence of mumps and mumps orchitis among males, 2000 apparently healthy male separatists ranging in age from 14 to 43 years were questioned carefully concerning a history of mumps, the age at which the disease had occurred, and whether orchitis had been a complication. Simultaneously the testes were carefully examined by inspection and palpation for softening and diminution in size indicative of atrophy. Only cases of orchitis which had been accompanied or shortly preceded by parotitis which was diagnosed as mumps were considered, and only cases of atrophy which developed as a direct aftermath of mumps orchitis were accepted for inclusion in the series.

The method of Schoenfeld and Beebe¹⁵ of comparing the size of the testis with standard models was not available so that decision as to whether

atrophy had taken place was made from the qualitative changes in the testes. Cases with atrophy were questioned and examined for symptoms or signs of the disability.

RESULTS

This group was a heterogeneous population representing various occupational and cultural backgrounds. The race and age distribution in the survey are given in figure 1. The median age was 21 years. The median time elapsing between this study and the time of occurrence of mumps was 11 years with a range of less than one year to 33 years. The median time elapsing since occurrence of orchitis in those individuals who had had this complication was only four years with a range of less than one year to 24 years.

Over one-half the series, 1086 individuals or 54.3 per cent, gave a history of having had mumps (see figure 2). The age at which mumps occurred is shown in table 4. The majority of cases, 80.4 per cent, had occurred before the fifteenth year, and the modal age at which the individual had acquired the infection was 10 years. Although mumps is uncommon before the age of three years, two cases in this study gave a history of having had mumps at the ages of 9 and 10 months respectively while another had been informed

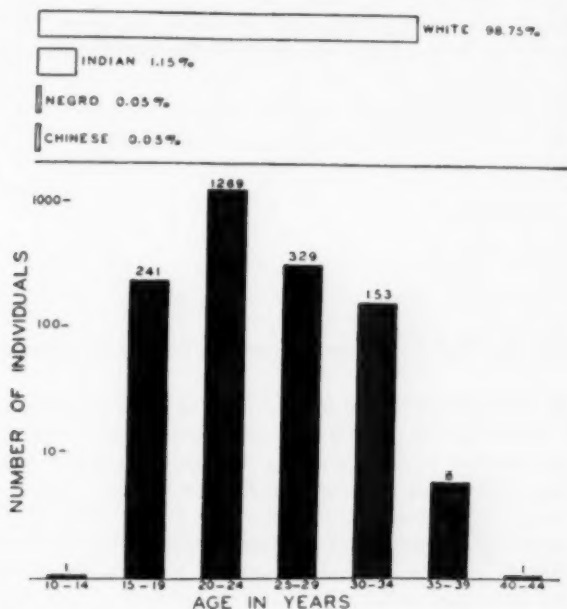


Fig. 1. Age and race distribution of 2000 males in mumps survey.

by parents that he had had mumps at 13 months. The greatest age of onset reported in the series was 30 years.

One attack of the disease confers an acquired immunity which is usually permanent. Macleod,¹⁰ however, reported 17 instances of second infection in his series and one which presumably was a third infection. In the present series only one individual reported having had a second infection. This was a 24-year-old white male who had had mumps on one side at 19 years and again on the opposite side at 23 years.

Only 53 individuals gave a history of having had mumps orchitis. While this constituted only 4.9 per cent of the entire series, it represented an incidence of 19.0 per cent of those having mumps after the age of 13 years.

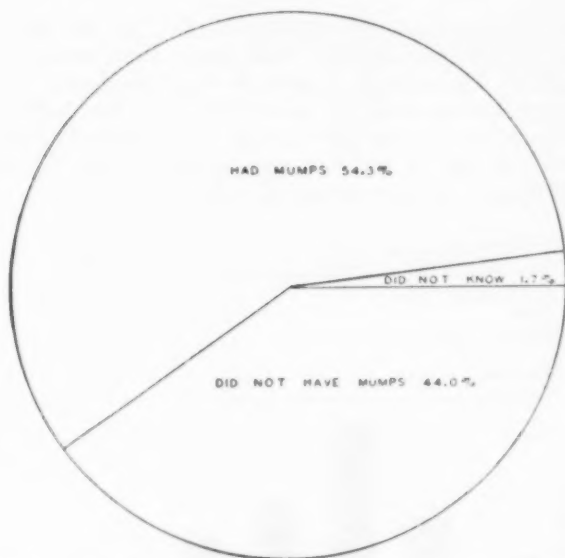


FIG. 2. Incidence of past history of mumps in a survey of 2000 males.

Although Wesselhoeft states that orchitis as a complication of mumps is confined to the age of puberty and adolescence, and while Candel encountered no instances of orchitis under the age of 10 years, in this series there were two individuals who reported mumps orchitis at eight years and two more who had contracted orchitis at 10 years. One of the former developed testicular atrophy. In another series of 49 individuals with mumps orchitis,²¹ one was 10 and another 11 years at the time of onset. Both of these developed subsequent testicular atrophy.

The age at which orchitis occurred in the present series is given in table 4.

TABLE IV

Age Distribution of Cases of Mumps, Orchitis and Testicular Atrophy in a Survey of 2000 Males
(These data are depicted graphically in figure 3).

Age in Years	Mumps		Orchitis		Atrophy	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
0-4	49	4.5%	0	0%	0	0%
5-9	428	39.5	2	3.8	1	5.2
10-14	396	36.4	10	18.9	4	21.0
15-19	178	16.4	35	66.0	12	63.3
20-24	27	2.5	5	9.4	2	10.5
25-29	6	0.5	1	1.9	0	0
30-34	2	0.2	0	0	0	0
Total	1,086	100.0%	53	100.0%	19	100.0%

Atrophy of one or both testicles was encountered in only 19 cases in the entire series. This was 35.8 per cent of the individuals who had contracted orchitis, a figure somewhat lower than that of others,^{4, 5, 20} and only 1.7 per cent of the entire series. The age at which those cases of orchitis occurred which progressed to testicular atrophy is given in table 4.

The orchitis was bilateral in one-third of the cases. In the remaining number orchitis had occurred about equally in the right and left testis. When atrophy developed following the orchitis, it did so bilaterally in only a few instances. Atrophy of the right testis occurred almost twice as often as it did in the left.

In another series of 39 cases of testicular atrophy following mumps orchitis,²¹ however, the two testes were equally involved when unilateral

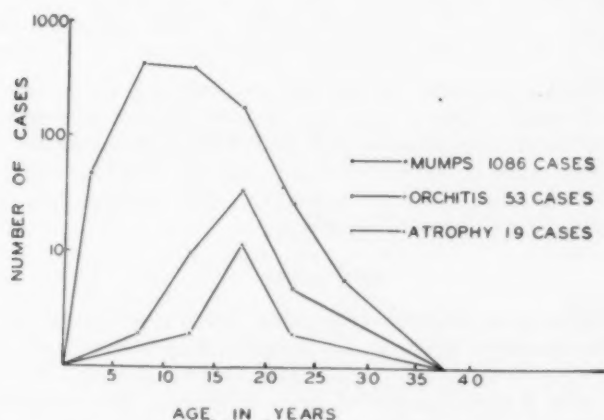


FIG. 3. Age of occurrence of mumps, mumps with orchitis, and mumps with orchitis followed by testicular atrophy in a survey of 2000 males.

TABLE V
Incidence of Right and Left and Bilateral Testicular Involvement in 102 Cases
of Mumps Orchitis and 58 Cases of Postorchitis Testicular Atrophy

	Involved by Orchitis		Underwent Atrophy	
	No.	Per Cent	No.	Per Cent
Right Testicle	36	35.3%	29	50.0%
Left Testicle	32	31.4	23	39.7
Both Testicles	34	33.3	6	10.3
Total	102	100.0%	58	100.0%

atrophy occurred. The data from the combined series are presented in table 5.

In addition to the 19 cases of atrophy due to mumps in the present study there were 25 individuals with testicular atrophy due to other causes. These are summarized in table 6. All of the 13 cases of atrophy in which no explanation could be furnished gave a history of mumps parotitis, but no direct causal relationship could be demonstrated.

TABLE VI
Etiology in 44 Cases of Testicular Atrophy Discovered in a Survey of 2000 Males

Etiology	Right	Left	Both	Total	
				No.	Per Cent
Mumps Orchitis	11	6	2	19	43%
Undetermined	7	2	4	13	30
Traumatic	8	2	1	11	25
Cryptorchidism	1	0	0	1	2
Total	27	10	7	44	100%

All the cases of testicular atrophy were asymptomatic except one or two who said on occasions they had noted a neuralgic type of pain referable to the testes. One 23-year-old white male with bilateral testicular atrophy for which no cause could be ascertained had a markedly feminine voice but no other altered secondary sexual characteristics. It is probable that this was not a true atrophy but a genital hypoplasia.

DISCUSSION

It is apparent from this and other studies that a relatively small proportion of cases of mumps infections are complicated by orchitis and that this complication is virtually limited to cases acquiring the infection after puberty. Moreover, only a small number of cases of mumps orchitis progress to testicular atrophy. The atrophy which follows mumps orchitis is asymptomatic and is confined to only one testis in the great majority of cases.

While mumps orchitis is an alarming, painful and uncomfortable complication of mumps in the post-puberal male, the only serious hazard which it holds is the possibility of rendering the individual partially or completely sterile. The results of a study on this will be presented in a subsequent paper.

CONCLUSIONS

In a heterogeneous series of 2000 males 14 to 43 years 54.3 per cent gave a history of having had mumps infection. Of these, 80.4 per cent had had the infection before the fifteenth year. The modal age of onset was found to have been 10 years.

Four and nine-tenths (4.9) per cent of all the cases of mumps and 19.0 per cent of cases of mumps which had onset after the thirteenth year gave a history of having had orchitis as a complication of the disease. This was right sided in 35.3 per cent, left sided in 31.4 per cent and bilateral in 33.3 per cent.

Testicular atrophy developed subsequently in 35.8 per cent of all cases of mumps orchitis. This constituted 1.7 per cent of all cases of mumps in the series and 6.8 per cent of cases which occurred after the thirteenth year. In a total of 58 cases of testicular atrophy following mumps orchitis the atrophy was right sided in 50.0 per cent, left sided in 39.7 per cent and bilateral in 10.3 per cent.

In the 44 cases of testicular atrophy from various causes found in this study mumps orchitis was the causative factor in 43 per cent.

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MUMPS ORCHITIS AND TESTICULAR ATROPHY. II. A FACTOR IN MALE STERILITY *

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DURING the past 50 years, increasing importance has been attached to the male factor in cases of barren marriage. It has been estimated that 12 per cent of all marriages are involuntarily sterile.²³ In 25 per cent of these the husband is at least partly to blame,¹⁰ and he is said to be solely at fault in 10 to 15 per cent.²² In a study of 200 cases of sterile marriage, Meaker²³ found the male to be at fault alone in 8 per cent, the female alone in 14 per cent, and both at fault in 78 per cent. When both were at fault, the male was chiefly to blame in 12 per cent, the female in 15 per cent, and both were equally to blame in 51 per cent.

A number of causes of sterility in the male have come to be recognized. These include anatomical anomalies such as undescended testes,^{6, 8, 24, 29} endocrine disorders, infections of the testes and epididymides such as tuberculosis, syphilis, gonorrhea and mumps, trauma of the testicles, exposure of the gonads to x-rays^{14, 30} and exposure to prolonged high temperature as in septic states.^{7, 20, 28, 29}

The soft, shrunken, atrophic testicle that occurs after mumps orchitis in 35 to 55 per cent of cases is seen commonly. In a previous study of 44 cases of obvious testicular atrophy found in a random examination of 2000 males 14 to 43 years, it was found that mumps orchitis had been the causative factor in 43 per cent. It was further shown that mumps is complicated by orchitis in one-fifth of all cases of mumps occurring in males after puberty.³⁴

There are few reports in the literature to indicate the incidence of sterility following mumps orchitis. Benard⁴ states that sterility following mumps orchitis is practically unknown. Moench²⁶ reported three cases of azoospermia following mumps orchitis with subsequent testicular atrophy, and Stengel³² cited two cases of male sterility undoubtedly due to mumps orchitis.

It is the purpose of this study to determine to what extent mumps orchitis impairs male fertility.

MATERIALS AND METHOD

Study of the seminal fluid as an aid in appraising the fertility of the male was suggested by Sims³¹ as early as 1868 and has now become a widely accredited diagnostic procedure. A number of technics for semen examination have been described.^{1, 3, 9, 12, 17, 22, 27, 33, 35} From analyses of semen speci-

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This study was made while the writer was on active duty with the United States Navy. National Institutes of Health Postdoctorate Research Fellow, Department of Medicine, New York Hospital—Cornell Medical Center.

mens and correlation with the fertility of the donors, certain standards for volume, pH, sperm count, motility and morphology have been adopted.^{3, 9, 10, 11, 12, 17, 18, 19, 25, 33, 36}

In this study, analyses of the seminal fluid in 49 males with a past history of mumps orchitis were made and compared to those of a control group of 91 normal males. All subjects in the series were volunteers. Each individual was carefully questioned for a history of any disorder which might affect reproductive function and examined for evidence of disease of the genital tract. No special examinations were employed other than the semen analysis. Where there was some factor either in the history or physical examination other than mumps orchitis which might have impaired fertility, the individual was not included in the series. Thus cases of hydrocele, undescended or severely injured testes, gonorrheal epididymitis, and illnesses which had been accompanied by high fever within the past three months were excluded. Cases of chronic prostatitis, on the other hand, were not disqualified, for this is not regarded as a cause of sterility.¹⁶

The specimens were obtained after 72 hours abstinence from intercourse in most cases. This promotes uniformity of specimens, for it is known that frequent ejaculation reduces volume and cell count.¹¹ The adverse effect of rubber condoms on sperm motility and viability has been recounted,²⁸ so all specimens were collected by ejaculation directly into a clean, dry, two ounce medicine glass. The donors were instructed to exercise care in collection of the sample so as not to lose any—especially the first half, since this has been found to contain 70 per cent of the total sperm as well as the more vigorous and healthy cells.^{5, 21}

In most of the controls only a single specimen was analyzed. If the specimen was a poor one, however, a subsequent determination was made after another period of 72 hours. This was checked against the first. If the second proved to be entirely normal, it was felt that the initial specimen could be discounted as being due to faulty preparation of the donor and collection of the specimen, and it was acknowledged that the individual was capable of producing a fertile specimen. In such case the better specimen was selected. If the second specimen likewise proved to be below normal standards, the two determinations were averaged.

In the cases with a history of mumps orchitis, two specimens from each donor were collected and the results averaged unless the two semen were disproportionately different, i.e. one very poor and the other entirely normal. In such case the better sample was selected for purposes of making the comparison with the control group. It was not possible to procure more than two specimens from a donor in this study.

The semen was examined as soon as liquefaction was complete. This required 10 to 30 minutes, an interval comparable to that found by others.^{11, 12} Volume was measured in a small, clean, dry glass cylinder graduate, 0.2 c.c. being routinely added to the observed meniscus to make up for the amount which adhered to the side of the medicine glass after pouring into the grad-

uate. Hotchkiss¹⁰ states that a seminal pool of less than 0.5 c.c. is inadequate to protect the sperm from the acid vaginal mucus. This volume was accepted as the lower limit of normal in this study.

Viscosity and turbidity were estimated simultaneously with volume determination. Specimens were graded normal, increased or decreased. Although it is conceivable that a highly viscid fluid might impede the progress of the sperm up the female genital tract, viscosity and turbidity were not included in the comparison of the characteristics of the semen of the control and test group, for it has not been settled that these two factors can be indicted as causes of sterility.

Motility was appraised both with regard to the grade of motility on a scale from 0 to 4+ and the per cent of sperm cells which were actively motile. The latter was determined in most instances by counting the number of actively motile sperm in a quadrant of the microscopic high power field and dividing by the total number of sperm in the quadrant. In specimens with a low sperm count, the entire field was counted, while in specimens with a high sperm density, it was necessary to make a 1:2 dilution of seminal fluid with physiological saline in order to make an accurate count. The quotient was expressed in per cent. Only a single observation on motility was made on these specimens. This was routinely made two hours after collection of the semen. For purposes of comparing the two groups as well as comparing the control group of this series with similar groups in the literature,^{9, 18} an arbitrary standard of motility was adopted so that if the grade of motility was below 3 minus or there were fewer than 40 per cent actively motile cells, motility was regarded as below normal.

The sperm count per c.c. was determined by stirring the seminal fluid thoroughly to make a homogeneous suspension of the cells. A 1:20 or a 1:10 dilution, depending on the sperm density of the specimen, was then made in a white blood cell pipet with a solution of 4 per cent sodium bicarbonate and 1 per cent phenol. After shaking the pipet for two minutes, a hemacytometer counting chamber was carefully loaded, the cells allowed to settle for five minutes, and the five diagonal squares in the center area counted as for a white blood cell count. Six ciphers were added to this number to give the total sperm per c.c. (This number was divided by two if the initial dilution had been 1:10.) The total sperm count was found by multiplying by the volume in c.c. of the semen.

While it requires only a single sperm to fertilize the ovum, it has been estimated that only a fraction of 1 per cent of the sperm cells in the semen are capable of union with the ovum.³⁷ Although there have been reported cases of pregnancy ensuing in wives whose husbands had sperm counts as low as 12 million per c.c., 60 million cells per c.c. is generally accepted as the lower level of normal.^{1, 9, 17, 18} This figure was accepted in the present study. No specimens were discredited on the basis of the total sperm count, for fertility is considered to depend more upon the sperm count per c.c. than upon the total count.¹⁷

In studying the morphology of the sperm, a smear of the seminal fluid was made in the fashion of a blood smear on a clean, dry glass microscope slide. This was allowed to dry in air, fixed briefly by heating, stained by Gram's method and examined by oil immersion. This method is known not to alter the morphology and to give good visualization of the spermatozoa if done properly.^{10, 21} The cells were classed simply as normal or abnormal in form in accordance with the accepted criteria of sperm morphology.^{21, 25, 35, 36} No differential count was made. A specimen was considered abnormal if there were more than 22 per cent abnormal forms. With higher proportions of abnormal cells conception is unlikely to occur, and, if it does occur, the likelihood of spontaneous interruption of pregnancy and the production of fetal malformations are increased.^{15, 25, 26, 36}

RESULTS

The control series consisted of 87 white and four Negro males ranging in age from 18 to 30 years with a median age of 19; 76 were single and 15 were married (figure 1). Only one of this group had been a parent.

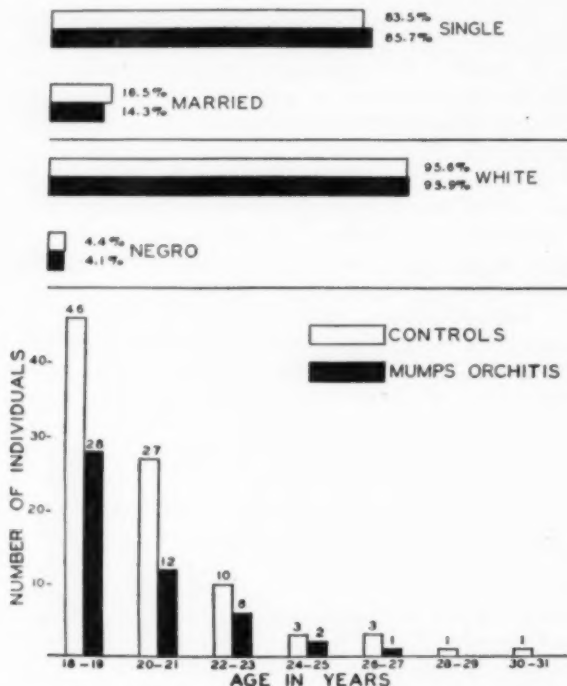


FIG. 1. Age, race, and marital distribution of 49 cases of mumps orchitis and 91 controls.

TABLE I
Testicular Involvement in 49 Cases of Mumps Orchitis

	Involved by Orchitis	Underwent Atrophy
Right Testis	22 cases	18 cases
Left Testis	15 cases	17 cases
Both Testes	12 cases	4 cases
Total	49 cases	39 cases

There was a history of mumps parotitis in 43, gonorrheal urethritis in 16, herniorrhaphy in four and syphilis in three individuals. In no instance had there been involvement of the testis or epididymis, however, and the scrotal contents were normal on examination.

The orchitis series consisted of 47 white and two Negro males ranging in age from 18 to 27 years with a median age of 19; 42 were single and seven were married (figure 1). Of this group four had been parents. There was a history of gonorrheal urethritis in nine, syphilis in two and herniorrhaphy in two individuals, but there had been no involvement of the testis or epididymis by any disease other than mumps. In this group mumps orchitis had been right sided in 22, left sided in 15 and bilateral in 12 cases. Some degree of testicular atrophy was apparent on examination in 39 individuals. This was right sided in 18, left sided in 17 and bilateral in four cases (table 1).

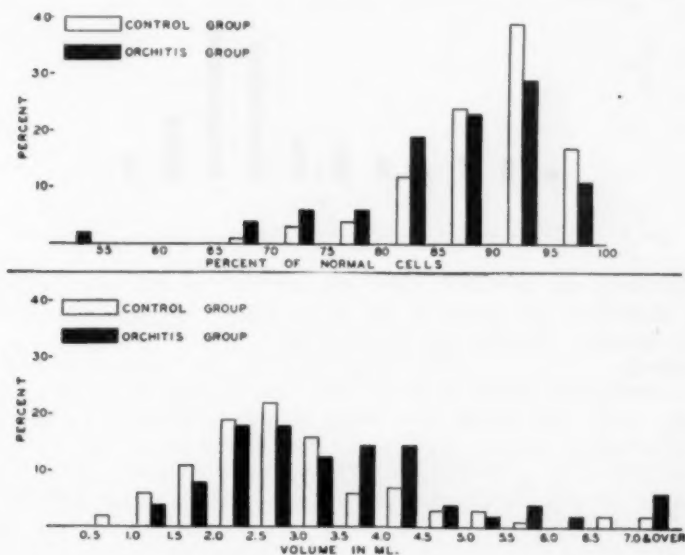


FIG. 2. Sperm morphology and semen volume in 49 cases of mumps orchitis and 91 controls.

Age at which the orchitis had occurred ranged from 10 to 27 years with a median of 16 years. The interval which had elapsed between the time of the orchitis and the time of this study ranged from a few months to nine years with a median of four years.

Volume: In the control group the volume of the seminal fluid ranged from 0.8 to 8.3 c.c. with a mean of 2.7 c.c.; in the orchitis group the range was 1.0 to 11.4 c.c. with a mean of 3.0 c.c. Thus all volumes were above the 0.5 c.c. minimum level in each group. No significant differences in volume were noted in the two groups (figure 2).

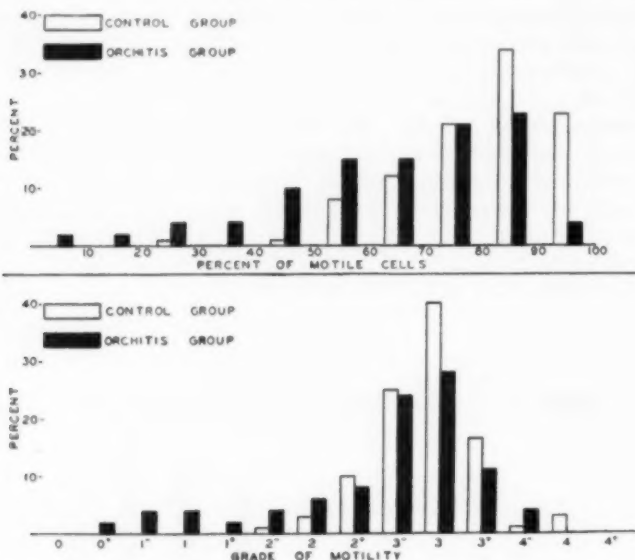


FIG. 3. Motility of spermatozoa in 49 cases of mumps orchitis and 91 controls.

Viscosity and Turbidity: There was essentially no difference in viscosity and turbidity of the semen in the two groups. Turbidity paralleled the sperm density of the specimen in most cases.

Motility: Grade of motility ranged from 2 — to 4 with a mode of 3 in the control group and from 0 + to 4 — with a mode of 3 in the orchitis group. Per cent of motile cells ranged from 28 to 98 per cent with a mean of 83 per cent in the control group and from 5 to 96 per cent with a mean of 68 per cent in the orchitis group. The control specimens exhibited a better grade of motility and a higher percentage of actively motile cells than the orchitis group (figure 3). There were 12 specimens (13 per cent) among the controls and 15 specimens (31 per cent) among the orchitis cases showing defective motility at two hours. Of the latter number there were 10 individuals with testicular atrophy and five without atrophy.

Sperm Count: Cell count ranged from 14.0 to 762.0 million per c.c. with a mean of 104.0 million in the control group and from 0 to 396.5 million per c.c. with a mean of 87.0 million in the orchitis group. Total count ranged from 28.0 to 2514.6 million with a mean of 308.0 million in the control group and from 0 to 1708.1 million with a mean of 264.6 million in the orchitis group. The only case of azoospermia encountered was a 19-year-old, single white male who had had bilateral parotitis and orchitis at 16 years with

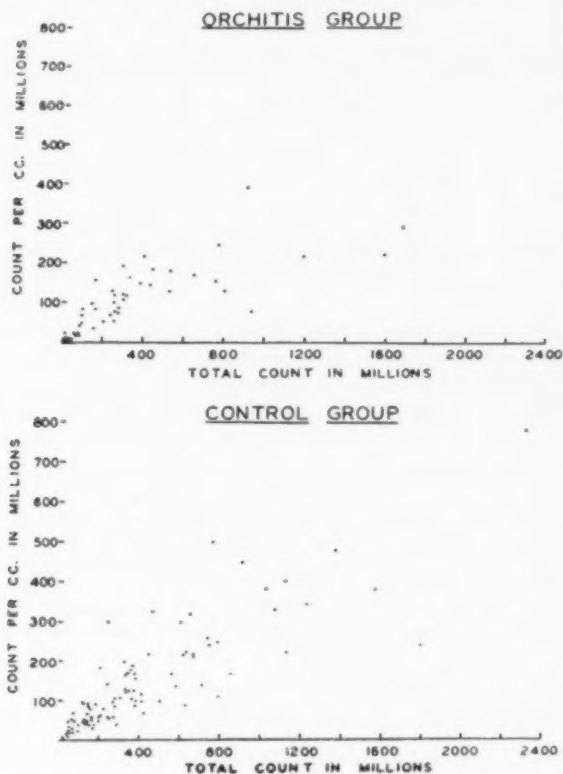


FIG. 4. Spermatozoa counts in 49 cases of mumps orchitis and 91 controls.

subsequent atrophy of the right testicle. He had 4.3 and 2.2 c.c. seminal fluid on two examinations but neither specimen contained spermatozoa. (This case was not included in the tabulation of motility and morphology.) There were nine controls and 18 orchitis cases of whom 15 showed evidence of atrophy who had cell counts below 60 million per c.c. This constituted 10 and 37 per cent of the two series respectively. The distribution of the specimens with respect to sperm count is given in figure 4.

Morphology: The proportion of normal cells ranged from 68 to 98 per cent with a mean of 91 per cent in the control series and from 54 to 98 per cent with a mean of 87 per cent in the orchitis group. The control specimens showed a slightly higher number of normal cells (figure 2). There were five specimens (6 per cent) among the controls and seven specimens (14 per cent) among the orchitis cases having more than 22 per cent abnormal forms. In the latter group there were five cases with testicular atrophy.

TABLE II

Compilation of Results of Semen Examinations in 91 Control and 49 Orchitis Cases

	Controls 91 Cases		Orchitis 49 Cases	
	Range	Mean	Range	Mean
Volume	0.8-8.3 c.c.	2.7 c.c.	1.0-11.4 c.c.	3.0 c.c.
Motility, grade	2- to 4	3	0+ to 4-	3
Motility, per cent	28-98%	83%	5-96%	68%
Sperm count per c.c.	14-762 mil.	104.0 mil.	0-396.5 mil.	87.0 mil.
Total sperm count	28-2514.6 mil.	308.0 mil.	0-1708.1 mil.	264.6 mil.
Morphology	68-98% normal	91% normal	54-98% normal	87% normal

A summary of the results is given in table 2.

The total number of specimens considered by the foregoing standards to be unsatisfactory in the control group was 35 or 38 per cent of the series. Of these 19 had low sperm counts, 11 had diminished motility and five had a combination of two or more disqualifying factors, i.e. low count, impaired motility, defective morphology (table 3). In the orchitis group there were 25 unsatisfactory specimens or 51 per cent of the series. Of these, three had low sperm counts, six had diminished motility, one had increased number of abnormal cell forms and 15 had a combination of two or more disqualifying factors (table 3). Of the 25 individuals in the orchitis group with unsatisfactory specimens there were 19 with some degree of testicular atrophy. This was the same proportion as that of the orchitis group as a whole.

There were four individuals in the orchitis group with evidence of atrophy of both testicles. All four had evidence of impaired fertility by

TABLE III

Summary of Disqualifying Factors in Unsatisfactory Semen Specimens from Control and Orchitis Groups

	Control Group	Orchitis Group
Low sperm count, fewer than 60 mil./c.c.	19	3
Impaired motility, less than 3- and/or 40% motile	11	6
Impaired morphology, fewer than 78% normal cells	0	1
Low count and impaired motility	0	9
Low count and impaired morphology	3	4
Impaired motility and morphology	1	1
Low count, impaired motility and impaired morphology	1	1
Total unsatisfactory specimens	35 (38 per cent)	25 (51 per cent)

TABLE IV

Results of Semen Examination in 4 Cases of Bilateral Testicular Atrophy from Mumps Orchitis

	1	2	3	4
Volume	4.2 c.c.	2.0 c.c.	2.7 c.c.	4.1 c.c.
Motility, grade	1—	3+	3—	1—
Motility, per cent	40%	66%	70%	13%
Sperm count per c.c.	9.2 mil.	12.5 mil.	14.5 mil.	19.0 mil.
Total sperm count	38.6 mil.	25.0 mil.	39.2 mil.	77.9 mil.
Morphology	82% normal	76% normal	81% normal	80% normal

the semen examination, and none had been a parent. The averaged results of the two examinations in each of these four individuals are presented in table 4. All were white males, and the interval from the time of the disease to the time of the study ranged from three to six years.

DISCUSSION

It was not the purpose of this study to establish the potential of fertility of individual cases. It must be appreciated that there can be a wide range of variation in repeated semen examinations in an individual so that a single examination may be insufficient to assess fertility.^{2, 3, 11, 32} Nevertheless, it has been determined from repeated semen analyses that the initial specimen is representative in almost every instance.¹⁸ Belding³ estimated that in 50 per cent of careful semen analyses duplication of results could be obtained with an error of only 7.6 per cent.

TABLE V

Comparison of Semen Analyses of Control Group, 100 Normal Males (MacLeod) and 200 Known Fertile Males (Hotchkiss)

	Hotchkiss 200 Cases		MacLeod 100 Cases		Controls 91 Cases	
	Range	Mean	Range	Mean	Range	Mean
Volume in c.c.	0.6-9.0	3.0	1.0-7.0	3.4	0.8-8.3	2.7
Motility, grade			1 to 4	3	2- to 4	3
Motility, per cent			10-80%	60%	28-98%	83%
Count per c.c., millions	2.25-544	120.5	1-458	134	14-762	104
Count, total, millions	2.82-2330	346.0	30-1291	435	28-2514.6	308
Morphology, normal oval or slightly tapering forms	65.8-98.8%	89.8%	75-94%	90%	68-98%	91%

Therefore, while it would be desirable to have had more specimens from the individuals in the two groups, it is felt that the present data are satisfactory for a comparison of results in the two series.

In general the results in the control series compare favorably with those in MacLeod's series of 100 normal young males and Hotchkiss' series of 200 known fertile males (table 5).

Hotchkiss' cases were males of known fertility; MacLeod's study was made in young male medical students. The control series in the present study was composed of young servicemen with widely varying social, educational and hereditary backgrounds. The incidence of venereal disease (21 per cent) in the past and alcoholic intake were probably much higher among the controls of this study. Only a few individuals were married and had produced children so that reproductive ability could not be checked with the findings of the seminal fluid examination as in Hotchkiss' study. Nevertheless the mean values as well as the upper and lower values in the control group approximate those of the other series.

Hotchkiss found 25 per cent of his group to have counts below 60 million per c.c.; MacLeod found 22 per cent of his group to have low sperm counts and 31 per cent to have unsatisfactory specimens when other criteria were considered, e.g. motility and morphology. When this is compared with the 38 per cent unsatisfactory specimens obtained from the 91 normal controls in this study, it becomes evident that approximately one-third of the normal male population come to be adjudged infertile on the basis of present standards of normal for seminal fluid examination.

Of course the values selected as normal for volume, cell count, motility and morphology are admittedly arbitrary. Failure to measure up to them does not signify sterility but rather a relative infertility. Absolute sterility cannot be said to exist unless there is azoospermia or complete necrospemia. So long as any motile sperm are found, a chance for fertilization exists. If a male of lowered fertility should be matched with a female of high fertility, chances for conception presumably would be increased.

Thus 25 per cent of Hotchkiss' known fertile males had cell counts under 60 million per c.c. Macomber¹⁷ cited cases of pregnancy occurring in women whose husbands had sperm counts as low as 12 million per c.c. Kleegman¹⁸ found the semen from one of 25 known fertile males to contain as high as 25 per cent abnormal sperm forms.

The difference between the proportion of unsatisfactory specimens in the mumps orchitis group and in the control group in this study was only 13 per cent. The chi square value of this sampling is 4.095, giving a value of *P* less than 0.05. Since this represents chance probability of less than 5 in 100, it is a statistically significant difference.* Therefore mumps orchitis can be expected to impair the fertility of one out of every 10 males in whom it occurs.

CONCLUSIONS

1. Thirty-eight per cent of a group of 91 normal males from 18 to 30 years were found to have semen of lower than normal standards as determined from analysis of sperm count, motility and morphology of the cells.
2. Fifty-one per cent of a group of 49 males from 18 to 27 years with a past history of mumps orchitis were found to have semen of lower than

* Mills, F. C.: Statistical methods, chapter xviii, 1938, H. Holt & Co., New York.

normal standards. There was encountered only one case of absolute sterility, i.e. azoospermia, in this group. Testicular atrophy was encountered no more frequently among the cases with abnormal semen specimens than it was found in the orchitis group as a whole.

3. Mumps orchitis operated to impair the fertility in 13 per cent of the individuals with a past history of the disease. This figure is statistically significant.

4. Since only 1.7 per cent of males with mumps contract orchitis and since only 13 per cent of those with orchitis were found to have impaired fertility attributable to this disability as adjudged by seminal fluid examination, mumps orchitis cannot be regarded as an important cause of sterility in the male population.

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THE MECHANICS OF DEFORMITIES OF THE HANDS IN ATROPHIC ARTHRITIS, AND A DISCUSSION OF THEIR PREVENTION AND CORRECTION *

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ONE of the earliest deformities in atrophic arthritis occurs in the hands. Characteristically, it develops into an ulnar deviation of the fingers with contractures at the metacarpophalangeal joints. This so greatly reduces the ability to use the hands that it may be regarded as one of the most distressing deformities of the disease. The morale of patients usually suffers less from their inability to walk than it does from inability to use the hands in some time-consuming occupation which might tend to shorten the long waking hours. Since more than 90 per cent of patients with this disease are women, this unsightly deformity wounds the patient's pride more than any other aspect of the disease. It cannot be hidden and constantly serves to advertise the affliction.

A lack of understanding of the mechanics of the typical ulnar deviation of the fingers has led to the development of certain practices in treatment which tend to increase it. This applies especially to the use of soft rubber balls as exercisers of the hands. It is believed that the wide application of the simple therapeutic exercises suggested below will do much to eliminate this annoying deformity in that great group of patients suffering from atrophic arthritis.

DESCRIPTION OF THE DEFORMITIES OF THE HANDS

For purposes of orientation, it may be well to describe briefly the several deformities of the hands in atrophic arthritis, and to consider them approximately in the order of their development. The earliest abnormality is that of puffy swellings either of the proximal interphalangeal joints, or of the metacarpophalangeal joints. The involved joints are held in slight flexion and this becomes the earliest deformity. Flexion deformities at the metacarpophalangeal joints are attended by well marked atrophy of the interosseus muscles of the hand. The next deformity, and by far the most typical one, is that of ulnar deviation of the fingers at the metacarpophalangeal joints. This begins gradually, and at first may be noticed only when the hand is semiflexed. In the late stages of this deformity, the fingers are pulled more and more laterally and the flexion upon the metacarpals increases. Subluxations are common. During the very late stages two

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Figures 1, 2, 3 and 4 are from Gray's Anatomy¹ and are presented by permission of the publishers, Lea & Febiger, Philadelphia.

ANATOMICAL CONSIDERATIONS

In order to understand the mechanics of these deformities it is necessary first to review the anatomy of the arm and hand with special reference to the extensor and flexor muscles of the fingers.

Flexion of the fingers is accomplished through the action of two muscles,—the Flexor digitorum sublimis and the Flexor digitorum profundus. The former arises from three heads,—humeral, ulnar and radial. The largest of these is the radial which extends along the oblique line of the bone through the upper half of its length. The manner of insertion of its four tendons concerns our problem intimately. Quoting from Gray's Anatomy,¹—"opposite the bases of the first phalanges each tendon divides into two slips to allow of the passage of the corresponding tendon of the Flexor digitorum profundus; the two slips then reunite, and form a grooved channel for the reception of the accompanying tendon of the Flexor digitorum profundus (figure 1). Finally the tendon divides and is inserted into the sides of the second phalanx about its middle." From this it is evident that the Flexor digitorum sublimis has no part in flexing the distal phalanges. Its action is first exerted in flexing the middle phalanx and later the proximal phalanx. It also plays a minor rôle in flexion of the elbow and the wrist.

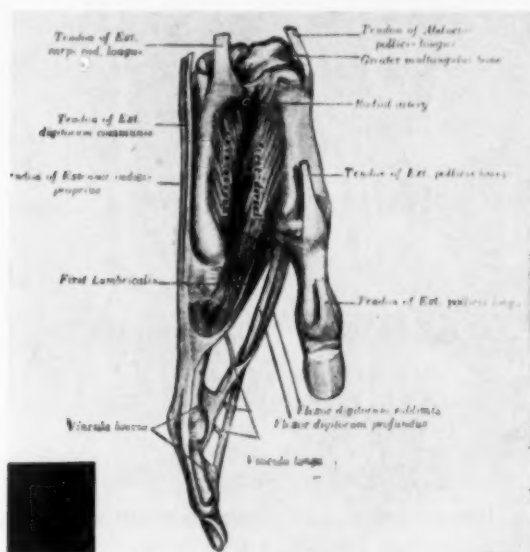


FIG. 2. The relation of the tendons of the deep and superficial flexors of the forefinger.

The Flexor digitorum profundus arises from the upper three-fourths of the volar and medial surfaces of the shaft of the ulna, and from some adjacent membranes and aponeuroses. It terminates in four tendons to the fingers. Opposite the first phalanges these tendons pass through the openings in the tendons of the Flexor digitorum sublimis, and are inserted into the bases of the terminal phalanges (figure 2). The Flexor digitorum profundus thus flexes the terminal phalanx but it does not come into play until the Flexor digitorum sublimis has contracted and semi-flexed the proximal interphalangeal joints.

The antagonists of these flexor muscles are the Extensor digitorum communis, the Interossei, and the Lumbricales. The Extensor digitorum communis arises from the lateral epicondyle of the humerus by the common tendon; from the intermuscular septa between it and the adjacent muscles; and from the antibrachial fascia. It divides into four tendons which pass under the dorsal carpal ligament and diverging on the back of the hand one goes to each of the fingers to be inserted into the second and third phalanges in the following special manner (figure 3). Opposite the metacarpophalangeal joints each tendon is bound to collateral ligaments to form the dorsal ligament of the joints. It then spreads out into an aponeurosis covering the dorsal

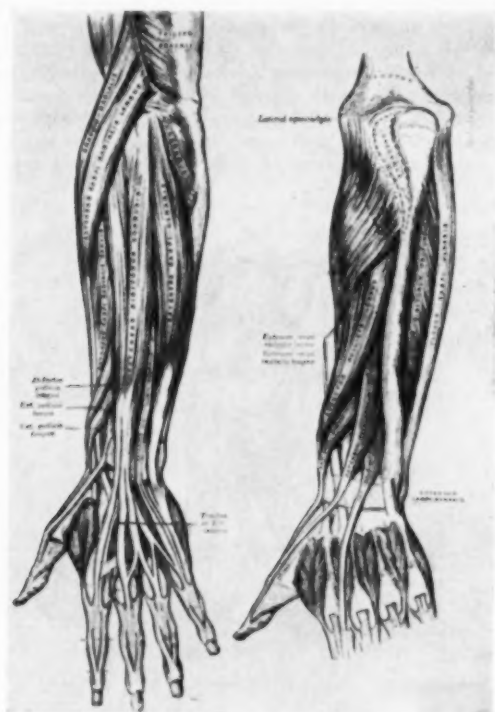


FIG. 3. Posterior surface of the forearm, superficial and deep muscles.

surface of the first phalanx where it is reinforced by receiving the tendons of the Interossei and the Lumbricales. Opposite the proximal interphalangeal joint this aponeurosis divides into three slips,—two lateral and one intermediate. The latter is inserted into the base of the second phalanx, while the lateral ones are continued along the sides of the second phalanx and again unite just proximal to their insertion into the dorsal surface of the terminal phalanx. It will be noted that the insertions are distributed in glove-like fashion along the fingers, and that each tendon as it crosses a digital joint furnishes it with a dorsal ligament. Into these ligaments and aponeuroses are inserted the tendons of the Interossei and the Lumbricales. The

Extensor digitorum communis is believed to act entirely on the first phalanges. The middle and terminal phalanges are extended mainly by the Interossei and the Lumbricales. The index finger and the fourth finger each have an additional small extensor muscle but these are unimportant in our consideration.

The Lumbricales are four small muscles arising from tendons of the Flexor digitorum profundus and passing to the radial sides of the fingers opposite the metacarpophalangeal joints to be inserted into the tendinous expansion of the Extensor digitorum communis covering the dorsal aspects of the fingers (figure 4). They flex the first phalanges at the metacarpophalangeal joints and extend the second and third phalanges.

There are four dorsal Interossei occupying the intervals between the metacarpal bones and each arising by two heads from the adjacent sides of the metacarpal bones. They are inserted into the bases of the first phalanges and into the aponeurosis of the tendons of the Extensor digitorum communis. The second and third are inserted into the sides of the middle finger, neutralizing their effects on this finger so that these four muscles abduct the fingers from an imaginary line drawn through the

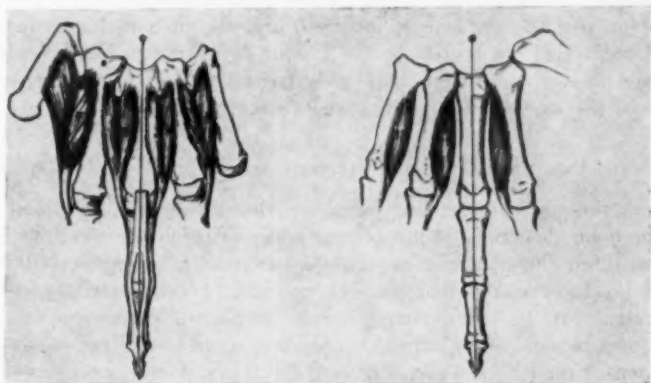


FIG. 4. The Interossei dorsales and volares of the left hand.

center of the middle finger. In addition to this and in conjunction with the lumbricales, they flex the first phalanges at the metacarpophalangeal joints and in consequence of their insertions into the expansions of the Extensor digitorum communis, they extend the second and third phalanges.

The volar Interossei are three in number and are smaller than the dorsal. They arise from the whole length of the metacarpal bone of the finger and are inserted into the side of the base of the first phalanx of the same finger and into an aponeurotic expansion of its Extensor digitorum communis tendon. They adduct the fingers to the imaginary line mentioned above as well as extend the fingers, as do the dorsal Interossei.

DEFORMITY AND DISUSE VS. MUSCLE TONE AND STRENGTH

In the hand flexion may be considered the motion of active work. It is usually carried out against resistance which requires, and develops

strength. The motion of extension is in part that of recoil. It is not carried out against resistance and requires little strength. Consequently the muscles of flexion are normally much larger and stronger than those of extension. As long as muscle tone is normal in both groups, and the digital joint ligaments strong, a balance exists which keeps the phalanges in alignment and the fingers straight. When inflammation appears in one of the digital joints a slight flexion of the joint is maintained to lessen the pain. This shortens the flexor and lengthens the extensor muscles. The latter impairs tone and strength more than does the former. Clinically a weakening of the extensors appears very early, and is accompanied by a remarkable atrophy of the dorsal Interossei. Since these muscles aid in completing extension of the fingers, they immediately fall into disuse because the fingers with their painful interphalangeal joints no longer are completely extended. Motions in flexion continue to be accomplished even in the presence of painful digital joints. These movements in fingers presenting contractures of the metacarpophalangeal and the proximal interphalangeal joints are carried out largely by the Flexor digitorum profundus which, as discussed above, comes into play after partial flexion is presented. This continued use would tend to maintain its strength and tone.

ANATOMIC IMBALANCE IN THE FLEXORS AND EXTENSORS OF THE HANDS

After this preliminary discussion, our thesis may now be stated. It is that the ulnar deformity in atrophic arthritis of the hands develops because of an anatomic imbalance in the antagonistic muscle groups which flex and extend the fingers, and that the flexors retain greater strength and more tonus than can be counteracted by the weakened extensors. Since the posterior ligaments of digital joints are made up of specialized expansions of the extensor tendons a weakening of these joints would be expected whenever weakening of the extensors occurs. A greater tonic pull of the flexors over the extensors upon fingers semi-flexed by arthritic contractures tends to deviate the fingers toward the ulnar side. It is suggested further that the Flexor digitorum profundus is the muscle chiefly accountable for this deformity. There are several reasons for this belief which might be stated partly in review here. First, in hands weakened by atrophic arthritis lateral deviation may be detected first at a stage of flexion of the fingers where this muscle begins its contraction. Second, flexion deformities of the fingers removes some of the necessity for the Flexor digitorum sublimis to initiate flexion and leaves much of flexion to be accomplished within the range of action normally covered by the Flexor digitorum profundus, thereby the better maintaining its tone. Third, the Flexor digitorum profundus has a focal point of insertion, and this point is the most distal of any of the muscles activating the fingers, so that the slightest off-center action could easily pull the fingers out of alignment.

PREVENTION AND CORRECTION OF LATERAL DEVIATION DEFORMITIES

If attenuated extensor muscles of the hand cannot hold the fingers in their normal position against the stronger tonus of the flexor muscles, exercises to strengthen the extensors are indicated. Any exercise which provides work for the extensors of the hand without at the same time activating the flexors should develop greater strength in the extensors and help to overcome the imbalance between the two groups of muscles. In actual application of these exercises it has been found that they correct the milder grades of this deformity and favorably influence all grades of it. Naturally the best results are obtained in the early deformities.

Exercises of this type are easily provided by instituting extension and abduction movements of the fingers either with or without resistance. If resistance to extending the fingers is offered by elastic bands, their recoil makes subsequent flexion an effortless movement which does not strengthen the flexors. Needless to say the squeezing of a rubber ball so frequently employed in these patients strengthens the flexors and creates further anatomic imbalance between flexors and extensors. It is about the worst exercise which could be devised for the hands in atrophic arthritis.

Early in our use of therapeutic exercises for the extensor muscles of the hand, extension of the fingers against resistance was employed through the use of a glove-exerciser described below. This is now used infrequently because it has been found that simpler procedures are adequate, and are more likely to be used regularly by the patient. The exercise recommended is that of having the patient make the greatest possible effort to abduct the fingers. He is simply asked to spread the fingers as widely as possible. This is an effort which cannot be made without extending the fingers at the same time, so that the *Interossei*, *Lumbricales* and the long extensors of the hand are all brought into action. It matters little whether much or little is accomplished by way of spreading or straightening the fingers. It is the contraction of the muscles which the effort requires that eventually brings about sufficient strengthening of them to influence favorably the deformities. If this is explained to the patient it does much to encourage him to undertake and persist in efforts even though they produce little movement of the fingers.

The amount of exercise must be adapted to each patient individually. This can easily be done by having him maintain the abduction-extension effort for from 10 to 30 seconds. After a short rest period the exercise may be repeated. Only a few such efforts should constitute the first exercise period. Gradually the exercises may be increased until the desired tone in the extensor muscles is acquired. The increase may be accomplished by increasing the number of movements, or by maintaining the extended position of the fingers for increasingly longer intervals, or by both. The exercise is so conveniently used by the patient that there is a tendency to

overdo it in the early stages of its use. Warning of this is soon given by the increased stiffness of the joints of the hands and soreness of the muscles of the arm. Prompt responses are the rule in the early stages of the ulnar deformity and complete correction results. Early improvement is noted by the patient even in the more severe grades of deformity and their enthusiasm assures the continued use of the exercises. While a definite statement of the prophylactic value of these exercises cannot be made, it is reasonable to assume that if they are effective in correcting deformities, they should be most important in preventing them. It is believed that the crippling ulnar deviation deformity can be prevented by a very few of these simple exercises daily.

THE GLOVE EXERCISES

An exerciser which is simple may be provided in a rather heavy leather glove, the fingers of which are held in a flexion greater than that of the patient's deformed hand by means of elastic bands attached distally to the fingertips of the glove and proximally to its palm, using a separate elastic for each finger. An old glove of the patient's which has the set of his hand and is not too stiff appears better than an especially provided new one. With the glove in place the patient extends and abducts the fingers against the resistance offered by the elastics. After maintaining this for from 10 to 30 seconds the fingers are allowed to return to their former flexed position solely by the recoil of the elastic bands. In all cases the elastic bands should be adjusted to the individual so as to allow some movement of the fingers in the extension efforts. There is the tendency for the patient to clench the hand at this stage of the exercise and he must be warned against this, since active employment of the flexors would defeat the purpose of the exercise. The fingers are simply extended and abducted against the resistance offered by the elastics and then allowed to come back to the former position without any effort at flexion on the part of the patient. After a short rest the exercise may be repeated. Only a few such movements should constitute the first exercise period. Gradually the exercises may be increased until the desired tone is acquired by the extensor muscles.

SUMMARY

1. An anatomic imbalance in the antagonistic muscles which flex and extend the fingers is presented as the primary cause of the ulnar deviation deformity of the hands in atrophic arthritis.
2. A simple therapeutic exercise to strengthen the extensor muscles is suggested to correct and prevent these deformities.

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THE TECHNIC AND DIAGNOSTIC VALUE OF ASPIRATION OF BONE MARROW FROM THE ILIAC CREST*

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In the spring of 1943, I saw a patient with roentgenologic evidence of a single metastatic lesion in the iliac bone, in whom the primary site of malignancy could not be established. In order to recover the neoplastic cells and possibly to identify them, I attempted aspiration of the iliac lesion. The aspiration proved easy to perform. However, in this particular case no neoplastic cells were recovered, but instead normal bone marrow was seen. Since that time my associates and I have performed iliac aspirations systematically on almost every patient of hematological interest admitted to the Montefiore Hospital.

The aim of the present communication is to describe in detail the technic of the iliac crest puncture, and to compare the diagnostic value of the iliac and the sternal bone marrow aspiration.

Ever since its introduction by Arinkin in 1928, the aspiration technic of the sternum has been almost the only source of bone marrow studies in clinical medicine. However, certain disadvantages of sternal bone marrow aspiration have become apparent. In the first place, this procedure, involving operation in the cardiac area, usually renders patients very apprehensive. Moreover, sternal aspiration is not without some danger, as the heart and great vessels are beneath the sternum, and the internal mammary arteries run parallel to its borders. Although in the literature only a few fatalities following sternal aspiration have been recorded, the actual number of fatal outcomes is probably much larger.

The technic of iliac aspiration, as presented here, seems to us to have some definite advantages over sternal aspiration.

TECHNIC OF ILIAC ASPIRATION

The preferable site for aspiration is the crest of the ilium posterior to the anterior superior spine. A needle, 16 gauge, 1 inch to 2.5 inches long, and furnished with a stylet, is used for puncture; a 20 c.c. tightly fitted syringe is used for aspiration. The patient usually lies on his back; in case of pronounced abdominal distention he is turned on his side.

The skin and subcutaneous tissues are infiltrated with 2 per cent novocaine solution, and the periosteum is slowly injected. The puncture is performed with the needle held in the sagittal plane of the body. The fingers

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of one hand are placed over the inner and outer plates of the iliac bone, stretching the skin over the crest; with pressure applied by the palm of the other hand, *the needle is directed from the top of the crest downwards* (and not from the outer surface of the iliac bone toward the abdominal cavity).



FIG. 1. Position of needle in the iliac bone.

A distinct "give" sensation is usually felt when the needle enters the medullary cavity. After the needle is firmly embedded, the stylet is withdrawn, the syringe attached and the plunger slowly withdrawn until the first drop of marrow fluid is visualized in the capillary end of the syringe. The material recovered may be used for enumeration of the total nucleated cell count, preparation of smears, and section studies.

The technical advantages of the iliac crest versus sternal puncture are as follows:

1. Safety: no serious injury can be sustained by any underlying organ.
2. Ease: usually the iliac puncture is less painful during and especially after its performance, and the patient is less apprehensive than when subjected to a puncture in the heart area.
3. Repeated aspirations: iliac crest punctures can easily be performed at frequent intervals on both sides of the body, and therefore are very suitable for serial bone marrow studies. This may be important especially in research studies of hematopoietic tissue. For instance, we were able to study the successive stages of maturation of megaloblasts in the bone marrow following folic acid therapy. In a case of pernicious anemia in relapse, iliac aspirations were repeated at 4 to 24 hour intervals for several days, though repetition of a sternal puncture was categorically refused by the patient.

One disadvantage of iliac aspiration is the occasional difficulty encountered in puncturing the bone, which at times may prove to be exceedingly hard. But even in these instances there is no danger in applying the necessary force provided that the technic as described is used.

THE CELLS OF THE ILIAC BONE MARROW

The iliac marrow has been studied in over 1,000 different cases showing normal and pathological findings; in about 300 of these cases simultaneous sternal marrow studies were also performed.

Normal Findings: In all instances with normal findings the iliac bone contained hematopoietically active marrow, and this was true also of old age groups (age range studied: 16 to 78 years). Except for a slightly lower total nucleated cell count, the normal values for the cell distribution (differential count) were found to have approximately the same range as those determined for sternal marrow.

Pathologic Conditions: Comparative studies of iliac and sternal bone marrow were performed in various instances of secondary anemia, hemolytic anemia, aplastic anemia, pernicious anemia, sprue, osteosclerotic anemia, Gaucher's disease, leukemias, multiple myeloma, various neoplastic diseases, and in various other conditions. In most of the cases studied the findings from both sources were parallel, and both aspirations have proved in these instances of equal diagnostic value.

However, in certain cases study of iliac marrow has proved of distinct diagnostic advantage as compared to the sternal marrow alone.

Diagnostic Advantages of Iliac Aspiration: The instances where iliac aspiration has provided more diagnostic information than the sternal technic were cases of infiltrative diseases of the bone marrow. It seems that in these instances the iliac bone was involved before the sternum. In other cases the reverse was true. Combined sternal and iliac bone marrow studies are

indicated wherever patchy character of the disease process in the marrow is suspected.

In the following instances the diagnosis was arrived at on the basis of iliac bone marrow aspiration:

1. Leukemia. In four cases the diagnosis of leukemia, confirmed at postmortem examination, was first made *in vivo* on the basis of iliac marrow studies. Diagnoses other than leukemia had been made previously when only sternal marrow was examined. Iliac aspiration first revealed a picture characteristic of leukemia, lymphatic or myelogenous; subsequently also the sternal bone marrow developed the same picture.

2. Multiple myeloma. In three instances the diagnosis was indicated by iliac marrow studies, while sternal marrow findings were not conclusive.

3. Also in some cases of aplastic anemia and osteosclerotic anemia ("spent polycythemia") the combined sternal and iliac bone marrow examination revealed the patchy character of the pathological process in the bone marrow: sternal aspiration yielded aplastic marrow while iliac aspiration showed active islands of hematopoiesis; in other cases the reverse was true.

4. In certain cases of malignant growths neoplastic cells were recovered in the bone marrow. This occurred more often in the iliac marrow than in that obtained by sternal aspiration. At times the sternal marrow was negative while the iliac was positive for neoplastic cells. This was seen in some cases of carcinoma of the prostate and of the breast. In one case iliac aspiration yielded ink-black material which on microscopic examination revealed the presence of numerous melanin-laden cells and the diagnosis of melanoma was made. The sternal aspiration did not reveal these cells.

SUMMARY

The technic of iliac bone marrow aspiration is described and its advantages indicated.

Study of the iliac bone marrow, alone or in combination with the sternal marrow, provided additional diagnostic information in some cases of infiltrative diseases of the bone marrow (leukemia, multiple myeloma, metastatic lesions). Uneven involvement of the skeleton in these cases with early infiltration of the ilium may explain the diagnostic value of the iliac aspiration.

THE TREATMENT OF BACTERIAL ENDOCARDITIS*

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DURING the last decade, the introduction and practical application of new chemical and antibiotic agents in the therapy of bacterial endocarditis have altered completely the outlook in this disease which formerly was considered to be almost universally fatal. Prior to the advent of the various sulfonamide compounds, no specific therapeutic agents were available, and spontaneous recoveries ranged about 1 per cent or less. In the years 1937 to 1943, the sulfonamide drugs, alone and with supplementary forms of treatment, provided cures in but 5.5 per cent of a large series of cases collected by Lichtman.¹ In 1943, the National Research Council² reported initially discouraging results in the treatment of 17 cases of bacterial endocarditis with penicillin, but the dosage schedule was quite small as judged by present standards.

In 1944 Loewe, Rosenblatt, Greene and Russell³ reported seven consecutive cases of subacute bacterial endocarditis treated successfully with penicillin and heparin. One year later, Dawson and Hunter⁴ and White, Mathews and Evans⁵ revealed recoveries of patients treated with penicillin without anticoagulant therapy.

During the last three years, although great optimism in the penicillin treatment of bacterial endocarditis has been expressed, many pressing problems remain for solution. A review of the literature⁴⁻²³ containing reports of five or more patients treated with penicillin reveals the fact that bacterial endocarditis is still a fatal disease in about 30 to 35 per cent of the patients. Little agreement is found among the various authors regarding the best route of administration, the dosage of penicillin, or the duration of therapy.

In the interest of providing additional clinical data on the problem of the treatment of bacterial endocarditis we deem it worthwhile to report the total experience of the Duke Hospital with this disease (table 1).

During the 17-year period, January 1930 to July 1947, the diagnosis of bacterial endocarditis was made in 138 instances. This group comprises only those cases in which the suggestive clinical picture was corroborated by two or more positive blood cultures or in which the diagnosis was revealed on postmortem examination. Those patients whose blood on culture yielded only a single colony per cubic centimeter of blood with or without the usual clinical picture were excluded. For purposes of clarity and analysis, the cases have been divided into three therapeutic periods.

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TABLE I

	No Specific Treatment		Sulfonamides				Penicillin		Ligation of Patent Ductus Arteriosus	
			Alone		With Fever Therapy					
	Cases	Cures	Cases	Cures	Cases	Cures	Cases	Cures	Cases	Cures
1930-1937	41	1 (2.4%)								
1938-1943	12	0	24	2 (8.3%)	17	2 (11.8%)				
1944							12	4 (33%)		
1945-(July) 1947	6	0					25	16 (64%)	1	1 (100%)
Total	59	1 (1.7%)	24	2 (8.3%)	17	2 (11.8%)	37	20 (54%)	1	1 (100%)

In the pre-sulfonamide period (1930 to 1937) the diagnosis of bacterial endocarditis was made in 41 instances, 39 ante mortem and two post mortem. During this period therapy was non-specific and unsatisfactory. These patients received a variety of remedies, including sodium cacodylate, neo-arsphenamine, gentian violet, autogenous vaccine, antisera, and fever therapy. In this group of 41 patients there was one spontaneous recovery (2.4 per cent). This patient is a 34-year-old white female who had rheumatic heart disease with mitral insufficiency, the clinical picture of bacterial endocarditis and two blood cultures, positive for six and eight colonies of *Streptococcus viridans* per cubic centimeter of blood. She received autogenous vaccine therapy and has been well for 12 years.

During the sulfonamide period (1938 to 1943) the diagnosis was made in 53 instances, 51 ante mortem and two post mortem. Ten patients received no specific therapy because of the existence of complicating factors such as severe congestive heart failure, renal insufficiency with uremia, or an idiosyncrasy to one of the sulfonamides. Forty-one patients were treated with one or more of the sulfonamides; 17 received the drug alone and 24 were given typhoid "H" antigen in addition. The sulfonamides used were sulfanilamide, disulfanilamide, neoprontosil, sulfapyridine, sulfathiazole, sulfamethylthiazole, sulfadiazine, and sulfamerazine. Reactions consisting of anorexia, nausea, vomiting, hematuria, headache, erythema, and leukopenia occurred in 29 patients but were not sufficient to require cessation of therapy. Two patients in the sulfonamide group were given heparin; neither recovered. One of these died of a cerebral hemorrhage, but at post-mortem examination it was impossible to relate the cerebral hemorrhage directly to heparin therapy. Although not proved, there was indirect evidence that it resulted from an infected embolus, because organisms and inflammatory cells were found in the meninges. In the entire sulfonamide group of 41 patients there were four recoveries,* 10 per cent (table 2). Of

* Two of these cases (Cases 1 and 2) have been reported previously.^{26, 27}

the 24 patients treated with the sulfonamide drugs alone, two are well, 8.3 per cent; of the 17 patients who received sulfonamide and fever therapy combined, two were cured, 11.8 per cent.

Lichtman's³ review of the literature indicated that 4 per cent of 489 patients treated with sulfonamides alone recovered. Of 45 patients treated with a combination of fever therapy (typhoid "H" antigen) and sulfonamides, 15.5 per cent recovered.

TABLE II

Case No.	Age	Sex	Duration of Symptoms	Cardiac Lesion	Infecting Organisms	Treatment	Duration of Treatment—Days	Duration of Cure—Years	Remarks
1	24	F	11 weeks	Pulmonary insufficiency	<i>Neisseria gonorrhoeae</i> , anaerobic streptococcus	216.2 gm. of sulfapyridine orally.	52	9	Well and active.
2	29	M	8 weeks	Rheumatic heart disease—mitral and aortic valves	<i>Streptococcus viridans</i>	42 gm. of sulfapyridine orally, 310 gm. of sodium sulfapyridine orally, 281 gm. of sodium sulfapyridine per rectum, 17.9 gm. of sodium sulfapyridine intravenously.	53	8½	Has had several recurrences of rheumatic fever since cure of bacterial endocarditis. At present well and active.
3	31	F	6 weeks	Rheumatic heart disease—mitral valve	<i>Streptococcus viridans</i>	80 gm. of sodium sulfapyridine orally, 32 gm. of sodium sulfapyridine intravenously, fever therapy with typhoid "H" antigen.	15	6½	Well and active.
4	20	M	12 weeks	Inter-ventricular septal defect	<i>Streptococcus viridans</i>	180 gm. of sulfapyridine orally, 24 gm. of sodium sulfapyridine intravenously, fever therapy with typhoid "H" antigen.		8½	Well and active.

During the penicillin period of therapy (1944 to 1947) the diagnosis of bacterial endocarditis was made in 44 patients. Six of these patients failed to receive penicillin because they refused to remain for treatment, preferred to be treated at home, or died before therapy was instituted. One patient was cured by ligation of a patent ductus arteriosus without chemotherapy and has been reported.²⁸ The remaining group of 37 patients was treated with penicillin, of whom 20 patients were cured, 54 per cent (table 3).

The ages of these 37 patients varied between 16 and 68 years; 27 were males and 10 were females.

Thirty-two patients had mitral or aortic lesions or combinations of the two valvular lesions. Three had congenital intraventricular septal defects. One had a ligated patent ductus (that had previously been ligated for bacterial endocarditis); one had no detectable valvular lesion on physical examination, and one had an infected left auricular thrombus.

Of the 37 patients treated with penicillin the infecting organisms were *Streptococcus viridans* in 31 patients. In the remaining six patients the organisms found were as follows: pneumococci in three instances, none of

TABLE III
Penicillin Cures

Case No.	Age Sex	Cardiac Lesion	Duration of Symptoms (Weeks)	Infecting Organism	Sensitivity of Organism to Penicillin Units per c.c.	Treatment					Duration of Cure (Months)	Remarks
						Initial Daily Dose, Units of Penicillin	Maximum Daily Dose, Units of Penicillin	Total Daily Dose, Units of Penicillin (Millions)	Duration of Penicillin Treatment (Days)	Sulfonamide Therapy		
6	16 F	Mitral valve	8	<i>Streptococcus viridans</i>	—	200,000	200,000	8.8	44	Yes—90 days ¹	36	Living and well.
10	19 F	Mitral valve	4	<i>Streptococcus viridans</i>	—	200,000 200,000 400,000	200,000 200,000 400,000	4.2 6.6 19.9	28 33 269	Yes Yes No	25	231 of total 269 days of penicillin therapy administered by patient at home. Now living and well.
11	35 M	Ligated patent ductus arteriosus ²	1	<i>Streptococcus viridans</i>	—	200,000	200,000	5.6	28	Yes—30 days ⁴	36	Previous ligation of patent ductus arteriosus for bacterial endocarditis. Recurrent infection two years later. Now living and well.
12	68 F	Mitral valve, auricular fibrillation	3	<i>Streptococcus viridans</i>	—	200,000	200,000	8.4	42	Yes—63 days ³	33	Congestive heart failure. Now living and well.
13	56 M	Mitral valve	5	<i>Streptococcus viridans</i>	—	200,000	200,000	5.6	28	Yes—10 days ¹	33	Living and well.
15	31 M	Aortic valve	6	Non-hemolytic and hemolytic <i>Streptococcus aureus</i>	—	200,000 200,000	200,000 200,000	2.8 11.5	14 210	Yes Yes	25	196 of total 210 days of penicillin therapy administered by patient at home. Now living and well.
16	19 F	Mitral valve	6	<i>Pneumococcus</i>	—	200,000	200,000	5.6	28	Yes—90 days ¹	33	Living and well.
18	25 F	Mitral valve	4	<i>Pneumococcus</i>	—	200,000	200,000	5.2	26	Yes—120 days ¹	27	Living and well.
19	34 M	Mitral valve	20	<i>Streptococcus viridans</i>	—	200,000	400,000	14.4	55	No		Congestive heart failure. Bacterial endocarditis healed at post mortem.
21	47 F	None detected ⁴	1	<i>Streptococcus viridans</i>	—	200,000	200,000	2.5	20	Yes—30 days ¹	27	Three consecutive cultures positive for 125, 125 and 125 colonies per c.c., respectively. Now living and well.
24	18 F	Mitral valve	1	<i>Streptococcus viridans</i>	—	400,000	400,000	19.9	56	Yes—Few days ¹	25	Living and well.

TABLE III—Continued

Case No.	Age	Sex	Cardiac Lesion	Duration of Symptoms (Weeks)	Infecting Organism	Sensitivity of Organism to Penicillin Units per c.c.	Treatment					Duration of Cure (Months)	Remarks
							Initial Daily Dosage Units of Penicillin	Maximum Daily Dosage Units of Penicillin	Total Dosage Units of Penicillin (Millions)	Duration of Penicillin Treatment (Days)	Sulfonamide Therapy		
25	39	F	Mitral valve	20	<i>Streptococcus viridans</i>	—	500,000	500,000	17	40	No	22	Living and well.
26	36	M	Mitral valve	12	<i>Streptococcus viridans</i>	—	200,000	200,000	3.6	18	Yes—70 days ¹	21	Refused additional penicillin. Now living and well.
27	38	M	Mitral valve	64	<i>Streptococcus viridans</i>	—	500,000	500,000	28	56	Yes—65 days ¹	21	Course of penicillin nine months before completion of therapy. No blood cultures. Now living and well.
31	42	M	Mitral valve	40	<i>Streptococcus viridans</i>	—	5,000,000	5,000,000	112	92	No	8	Congestive heart failure one month after cessation of therapy. Had penicillin therapy before hospitalization. Now living and well.
32	29	M	Inter-ventricular septal defect	7	<i>Streptococcus viridans</i>	0.5	480,000	1,660,000	64.7	37	Yes	8	Living and well.
33	35	M	Mitral valve	84	<i>Streptococcus viridans</i>	—	980,000	980,000	29.4	30	No	8	Living and well.
34	43	M	Mitral valve	10	<i>Streptococcus viridans</i>	0.1	1,020,000	2,040,000	50.7	42	No	8	Living and well.
35	67	M	Mitral valve	16	<i>Streptococcus viridans</i>	0.005	1,200,000	1,200,000	25.2	21	No.	7	Living and well.
36	42	M	Mitral valve	12	<i>Streptococcus viridans</i>	0.001	1,100,000 ² 800,000	1,100,000 2,400,000	21.9 100 121.9	21 54 75	No Yes—35 days ³	6	Living and well.

¹ After completion of penicillin therapy.² Each of these patients relapsed and received one or more additional courses of penicillin as shown.³ Non-rheumatic lesions. The remaining cardiac lesions were rheumatic in origin.

which were typed, non-hemolytic *Staphylococcus aureus* in one, both hemolytic and non-hemolytic *Staphylococcus aureus* in one, and hemolytic *Staphylococcus aureus* in one. Of the 20 patients who were cured, 17 were infected with *Streptococcus viridans*, two with pneumococci and one with both hemolytic and non-hemolytic *Staphylococcus aureus* organisms.

When penicillin first became available to us in small quantities for the treatment of bacterial endocarditis in February, 1944, the initial dosage schedule was begun at a level of 40,000 units per day. As the supply of penicillin became more abundant, the daily dose was increased to 200,000 units per day. The method of administration of penicillin generally combined a continuous intravenous drip with intermittent intramuscular injections. The usual schedule consisted of a continuous intravenous drip during the day for the first week with intermittent intramuscular injections every three hours during the night. After the first week intermittent intramuscular injections every three hours day and night replaced the intravenous route. During 1944 penicillin therapy was initiated in 12 patients and each received a course of sulfonamide after the completion of penicillin therapy. Of these, four patients (Cases 6, 10, 11, and 12) recovered, 33 per cent (table 3); each received an initial daily dose of 200,000 units of penicillin. Of the remaining eight patients in the failure group, therapy was begun in six (Cases 1, 2, 3, 4, 5, and 9) at levels below 200,000 units per day (table 4).

During the year 1945 and thereafter as penicillin became more plentiful, patients were treated with 200,000 to 500,000 units per day. When penicillin became available in unlimited quantities, considerably larger dosages of penicillin were administered, particularly in those cases which were initially unresponsive to penicillin therapy or whose organisms were found to be penicillin resistant. During this period therapy was initiated in 25 patients, of which 16 were cured, 64 per cent.

Of the entire group of 20 patients who were cured nine received 200,000 units of penicillin per day; six patients received 400,000 to 500,000 units per day; and five patients received from 980,000 to 5,000,000 units per day. These figures represent maximum daily dosages. The total dosages were as follows: eight received less than 10,000,000 units of penicillin; four patients received 10,000,000 to 20,000,000 units; five patients received 25,000,000 to 51,000,000 units; and three patients received 64,000,000 to 121,000,000 units as their total dosage.

Of the 19 cures that are living 10 have been well for more than two years; three patients have been well for one to two years; and six have been well for at least six months. Case 19 presented evidence of healed bacterial endocarditis at postmortem examination. The autopsy revealed a mural thrombus in the left auricle as a result of infarction of the left auricle. Portions of this thrombus produced emboli to the brain and colon. Following infarction of the colon, peritonitis developed. Meanwhile the patient went into congestive heart failure. The combination of congestion and peritonitis

TABLE IV
Penicillin Failures

Case No.	Age	Sex	Cardiac Lesion	Duration of Symptoms (Weeks)	Infecting Organism	Sensitivity of Organism to Penicillin Units per c.c.	Treatment					Cause of Death	Remarks
							Initial Daily Dose, Units of Penicillin	Maximum Daily Dose, Units of Penicillin	Total Daily Dose, Units of Penicillin (Millions)	Duration of Treatment (Days)	Sulfonamide Therapy		
1	20	F	Mitral valve	28	<i>Streptococcus viridans</i>	—	40,000	80,000	1.9	36	Yes	Pulmonary embolus	Congestive heart failure. Blood cultures negative during penicillin therapy.
2	57	M	Mitral valve	4	<i>Streptococcus viridans</i>	—	40,000	120,000	1.6	23	Yes	Cerebral embolus	Blood culture and fever not responsive to penicillin.
3	33	M	Aortic valve	12	<i>Streptococcus viridans</i>	—	40,000	200,000	4.4	25	Yes	Not known ¹	Blood cultures and fever not responsive to penicillin.
4	20	M	Inter-ventricular septal defect ²	8	<i>Streptococcus viridans</i>	—	100,000	200,000	8.2	50	Yes	Not known ¹	Congestive heart failure. Blood cultures and fever not responsive to penicillin.
5	63	M	Aortic valve	24	<i>Streptococcus viridans</i>	—	100,000 200,000	200,000 200,000	6.6 5 11.6	38 25 — 63	Yes ³ Yes ³	Not known ¹	Blood cultures and fever not responsive to penicillin.
7	21	M	Aortic and mitral valves	8	<i>Streptococcus viridans</i>	—	200,000 200,000 400,000	200,000 200,000 400,000	5.6 16 29.3 50.9	28 86 161 269	Yes ³ Yes ³ No	Anesthesia for ligation of mycotic aneurysm	Congestive heart failure. Continued positive blood cultures on penicillin.
8	26	M	Aortic and mitral valves	12	<i>Streptococcus viridans</i>	—	200,000 200,000 400,000 (2,000,000)	200,000 200,000 400,000 2,000,000	4.2 3.0 4.8 64.2	21 26 11 27 ⁴ 87	Yes ³ Yes ³ Yes ³	Congestive heart failure	Received course of penicillin and sulfonamides before hospitalization.
9	56	M	Thrombus in left auricle	2	<i>Pneumococcus</i>	—	80,000	200,000	1.5	11	Yes—before penicillin therapy	Toxemia	Thrombus was infected and attached to endocardial surface of left auricle producing a functional mitral stenosis at post mortem.
14	40	M	Mitral valve	32	<i>Streptococcus viridans</i>	— (6)	200,000 400,000 12,000,000 20,000,000	400,000 400,000 18,000,000 20,000,000	13.4 192 118.2 1490.4	44 486 84 ⁴ — 613	Yes No	Congestive heart failure ¹	Previous course of penicillin and sulfonamides. Negative blood cultures during therapy.

TABLE IV—Continued

Case No.	Age	Sex	Cardiac Lesion	Duration of Symptoms (Weeks)	Infecting Organism	Sensitivity of Organism to Penicillin Units per c.c.	Treatment				Cause of Death	Remarks
							Initial Daily Dosage Units of Penicillin	Maximum Daily Dosage Units of Penicillin	Total Dosage Units of Penicillin (Millions)	Duration of Treatment (Days)	Sulfonamide Therapy	
17	31	M	Aortic and mitral valves	12	<i>Streptococcus viridans</i>	—	200,000	600,000	28	98	No	Sulfonamides before hospitalization. Negative blood cultures but continued fever during therapy.
20	41	M	Mitral valve	10	<i>Streptococcus viridans</i>	—	200,000	600,000	43	125	No	Continued positive blood cultures on penicillin.
22	34	M	Mitral valve	12	<i>Streptococcus viridans</i>	—	200,000 100,000	200,000 100,000	5 1.3 — 6.3	25 13 — 38	Yes No	Negative blood cultures during penicillin therapy.
23	17	M	Aortic and mitral valves	1	Hemolytic <i>Streptococcus aureus</i>	—	400,000	400,000	11.6	29	No	Congestive heart failure. Negative blood cultures during penicillin therapy.
28	40	M	Mitral valve	3	<i>Streptococcus viridans</i>	Not inhibited by 1.0	400,000	400,000	11.6	36	Yes ^a	Presumed well at discharge. Died one month later at home on sulfonamide therapy.
29	35	F	Mitral valve	24	Non-hemolytic <i>Streptococcus aureus</i>	—	600,000	3,000,000	97.4	51	No	Congestive heart failure. Sulfonamide and penicillin therapy before hospitalization.
30	32	M	Aortic and mitral valves	16	<i>Streptococcus viridans</i>	.25 ^a	1,500,000 10,000,000	5,000,000 10,000,000	97.5 292.5 — 390	105 63 — 168	No No	Continued positive blood cultures on penicillin. Penicillin continued at home. Congestive heart failure.
37	18	M	Aortic valve	16	<i>Streptococcus viridans</i>	—	1,300,000	2,000,000	20	15	Yes	Blood cultures sterile during therapy.

¹ Died at home.² Non-rheumatic lesions. The remaining cardiac lesions were rheumatic in origin.³ After completion of penicillin therapy.⁴ Therapy received in another hospital after discharge.⁵ 365 of 480 days of penicillin therapy administered at home by patient.⁶ Repeated sensitivity studies J, 1.0 and 24 units per c.c. at 6 weeks, 18 weeks and 28 weeks later, respectively.

led to the development of thrombi in the pelvic veins with resulting pulmonary emboli and pulmonary infarction. The infarction of the colon also led to an *E. coli* septicemia proved by blood cultures two days before death. There was evidence of a healed bacterial endocarditis on the mitral valve at autopsy.

Three well patients received one or more courses of penicillin because of a recurrence of positive blood cultures while under sulfonamide therapy after cessation of penicillin treatment. Two patients (Cases 10 and 15) were taught to administer penicillin to themselves at home in order that they might receive penicillin over prolonged periods of time in an effort to control their disease, even though a cure might not be effected. After a period of several months of successful progress, penicillin was decreased gradually to 25,000 units per day and recovery ensued. Case 10 received penicillin for 330 days out of 365 consecutive days. Case 15 received penicillin for 287 days out of 297 consecutive days. Both have been well for 25 months.

Failures have been observed in 17 patients treated with penicillin. It has not been possible to determine the cause of treatment failure in each individual instance. The first four patients of the series were treated with obviously inadequate doses of penicillin when this drug was quite scarce. Many of the patients have died at home without adequate observations. It seems quite probable that fatal emboli, pulmonary, cerebral or general, have been the most frequent causes of death. Two of our failures (Cases 8 and 14) have gone to other clinics and have been treated with tremendous amounts of penicillin (2,000,000 and 20,000,000 units per day) with the same fatal outcome. Eight of our patients were presumed to be cured only to relapse in a few days on discontinuing antibiotic therapy, and five of these were failures even after repeated courses of therapy. An analysis of our failures offers the premise that larger initial doses of penicillin might have been effective had they been instituted before the development of penicillin resistance by the organism. Case 7 that developed a mycotic aneurysm, Case 8 that died of congestive failure, Case 23 that died of multiple septic emboli might have had different outcomes had the initial penicillin dosage been adequate. Three patients, Cases 8, 29, and 30, had courses of small-dose penicillin therapy prior to hospitalization. It is of interest that three patients (Cases 14, 29, and 30) received enormous amounts of penicillin—1490.4 million units, 97.4 million units, and 390 million units, respectively, without recovery.

Various authors have emphasized the importance of the route of the administration of penicillin. Gerber, Schwartzman, and Baehr⁷ advocated intermittent intramuscular injections of large doses of penicillin at three-hour intervals because higher peaks of plasma penicillin levels were obtained, thereby favoring penetration of penicillin into the bacterial vegetations. They favored additional massive booster doses each day. Loewe¹⁰ emphasized the importance of continuous intravenous drip in order to maintain a constant penicillin plasma level. From the literature⁴⁻²⁵ (table 5) and our own series, we have collected 619 patients treated with penicillin and

TABLE V

Report	Total Cases	Total Cures	Route of Administration								With Anticoagulants		Without Anticoagulants	
			Continuous Intravenous or Intramuscular		Intermittent Intramuscular		Combinations							
			Cases	Cures	Cases	Cures	Cases	Cures	Cases	Cures	Cases	Cures	Cases	Cures
			Cases	Cures	Cases	Cures	Cases	Cures	Cases	Cures	Cases	Cures	Cases	Cures
Dawson and Hunter—First report ¹ Second report ^{1a}	20 15	15 15	5 15	4 15	7 9	5 4	8 6	13	15	13	5 15	2 15		
White, Mathews and Evans ²	9	4									9	4		
Bloomfield, Armstrong and Kirby—First report ³	11	9									11	9		
Bloomfield and Halpern—Second report ^{3a}	18	18									18	18		
Gerber, Schwartzman and Baehr ⁷	29	22			29	22	18	0	4	0	25	22		
Paulin and McLoughlin ⁴	6	3			6	3					6	3		
Meads, Harris and Finland ⁵	9	7			9	7					9	7		
Loewe ⁶	54	40	54	40					54	40				
Goerner, Geiger and Blake ¹¹	12	11	12	11							12	11		
Flippin, Mayock, Murphy and Wolferth ¹²	20	12	20	12							20	12		
Favour, Janeway, Gibson and Levine ¹⁴	17	11	17	11							17	11		
Christie ¹³	147	81	73	40	74	41					147	81		
Glaser, Smith, Harford and Wood ¹⁷	28	19			28	19	6	4			28	19		
Mokotoff, Brains, Katz and Howell ¹⁸	17	14			11	10			9	7	17	14		
Levy and McKrill ¹⁶	11	8	6	4	5	4	12	11			2	1		
McMillan ¹⁵	12	11									12	11		
Seabury ²¹	12	7	12	7							12	7		
Thill and Meyer ²²	22	17			22	17			13	11	9	6		
Priest, Smith and McGee ²³	34	22	34	22					12	4	22	18		
Oglesby, Bland and White ²⁴	44	37									44	37		
Tumulty and Harvey ²⁵	35	22	3	3	25	16	7	3			35	22		
Present Series	37	20					37	20			37	20		
Total	619	425 (68.7%)	251	169 (67.3%)	225	148 (65.8%)	101	71 (70.3%)	107	75 (70.1%)	512	350 (68.4%)		

found a recovery rate of 68.7 per cent (425 of 619 patients). With the use of continuous drip therapy, either intravenous or intramuscular, 67.3 per cent recovered (169 of 259 patients); with intermittent intramuscular injection at one to three-hour intervals 65.8 per cent recovered (148 of 225 patients); with varied combinations of the above 70.3 per cent recovered (71 of 101 patients).

These figures demonstrate that the route of administration of penicillin makes little difference in the final results of therapy. The comfort of the patient should be considered when the initial choice is made. Patients have recovered following the use of daily injections of penicillin in peanut oil and beeswax²⁹ and even the oral administration of penicillin.³⁰ However, Oglesby, Bland and White²⁴ mention one case treated with peanut oil and beeswax for one month which at autopsy manifested large gluteal abscesses with extensive muscle necrosis at the sites of injection. Cultures revealed similar organisms in the abscesses and in the blood stream. The oral administration of penicillin is not practical if high plasma levels of penicillin are required in dealing with resistant organisms.

Sensitivity studies with the infecting organisms *in vitro* are extremely important before instituting therapy in order to estimate more accurately the effective daily dosage of penicillin. Christie¹⁶ found that in 16 patients who had had more than one course of penicillin, two showed evidence of increasing resistance both increasing threefold. Hunter³¹ mentions in his series of 50 patients one instance of the clearcut development of penicillin resistance. Priest, Smith, and McGee²³ suggest that *in vitro* sensitivity studies are only a rough guide to daily dosage and have little bearing on the outcome. Glaser, Smith, Harford, and Wood¹⁷ felt that *in vitro* studies performed by various methods were not consistent enough to predicate the exact dosage of penicillin, although two strains were found to be relatively resistant.

In one of our patients (Case 30) the sensitivity of the organism changed from .25 unit of penicillin per c.c. to 24 units of penicillin per c.c. in 28 weeks, even though the initial daily dose of penicillin was begun at 1,500,000 units per day, and was increased in a few days to 5,000,000 units per day. The organism from one of our cases cured (Case 36) increased its resistance from .001 to 1.0 unit of penicillin per c.c. in four weeks.

There is sufficient evidence that a bacterial organism may develop increasing resistance to penicillin so that it becomes of paramount importance to provide adequate dosage in the initial plan of therapy. If the patient with bacterial endocarditis is started on inadequate dosage, the chance of recovery may be jeopardized and treatment prolonged unnecessarily.

The daily dosage of penicillin should depend on the sensitivity of the organism and whether the patient has had previous therapy. Hunter³¹ reported a cure treated with penicillin (20,000,000 units a day) and streptomycin in which it required eight units of penicillin per c.c. of broth in order to inhibit the organism *in vitro*. Tumulty and Harvey²⁸ mention one instance in which 10 units of penicillin per c.c. were required to inhibit the

infecting organism; successful treatment followed the use of 4,800,000 units of penicillin per day for 42 days.

Loewe,¹⁰ Dawson and Hunter,¹⁵ and Mokotoff, Brams, Katz, and Howell¹⁸ have suggested that the plasma level be 4 to 10 times the amount of penicillin required to inhibit the growth of the organism. In some instances of highly resistant organisms very high plasma levels of penicillin then would be required. Intravenous para-amino hippurate³² has been used in conjunction with penicillin in the treatment of subacute bacterial endocarditis to enhance the penicillin blood level. Para-amino hippurate has been limited in its usefulness because of the necessity of administering large amounts by constant intravenous infusion.

More recently caronamide³³ has been administered orally with penicillin in order to increase the penicillin plasma level. Case 30 received 24 gm. of retentin (a form of caronamide) a day for nine days in conjunction with 50,000 units of penicillin given every two hours by intramuscular injection. During the retentin therapy the patient remained quite nauseated and values obtained one hour after a penicillin injection ranged between .6 and .8 unit of penicillin per c.c. of plasma. After discontinuing retentin the level varied between .55 and .65 unit of penicillin per c.c. of plasma. In this single instance retentin therapy was not helpful. Hagedorn and Scheifley³⁴ reported a similar instance in which 12 gm. of retentin a day did not significantly change the penicillin content of the plasma in a patient with subacute bacterial endocarditis.

In the first report of seven cases by Loewe and his associates,³ heparin was used simultaneously with penicillin. Friedman, Hamburger, and Katz³⁵ and Kelson and White³⁶ in 1939 suggested the use of heparin in conjunction with specific therapy in the treatment of subacute bacterial endocarditis in an effort to prevent fibrin deposition on the valvular vegetations. Priest, Smith, and McGee³⁷ have shown that fibrin deposits on valves are unaffected by anticoagulant therapy and reported two cases in which anticoagulant therapy may have been related to fatal hemorrhage. A review of the literature reveals that of 107 patients who received anticoagulant therapy 75 (70.1 per cent) recovered. Of 512 patients, 350 (68.4 per cent) have recovered without anticoagulant therapy. It appears that anticoagulant therapy offers no significant advantage in the treatment of bacterial endocarditis and may be dangerous.

Various authors have advocated from two to eight weeks of penicillin therapy. Dawson and Hunter⁴ point out that five of their successful cases received penicillin for less than two weeks. Meads, Harris, and Finland⁹ suggest two weeks of penicillin therapy as being sufficient. Christie,¹⁶ and Priest, Smith, and McGee²³ favor four weeks of therapy. Thill and Meyer²² advise a minimum of six weeks of therapy. Bloomfield and Halpern¹³ recommend two months of therapy. Loewe¹⁰ suggests that the duration of therapy should depend upon the duration of symptoms. In this series, the duration of penicillin treatment has depended on the general condition of the

patient, the penicillin sensitivity of the infecting organism, and whether the patient had received previous antibiotic therapy. The duration of penicillin therapy in the group of cures was: three weeks or less in three patients, three to four weeks in four patients, four to six weeks in seven patients, and more than six weeks in seven patients. Ten of the 17 failures received more than six weeks of penicillin therapy. At present, four to six weeks of penicillin therapy are being given in order to be conservative.

SUMMARY

An analysis of 138 instances of bacterial endocarditis has been presented. This report represents the total experience of the Duke Hospital in the treatment of this disease by various methods.

During the pre-sulfonamide period (1930 to 1937), when therapy was non-specific and unsatisfactory, 41 instances of bacterial endocarditis were observed. Of these one patient survived following the use of autogenous vaccine therapy.

In the sulfonamide period (1938 to 1943), the diagnosis of bacterial endocarditis was made in 51 instances. Treatment with one or more of the sulfonamides was administered to 41 patients. Four patients survived, a recovery rate of 10 per cent. Of 24 patients who received the sulfonamides, two are well (8.3 per cent); of 17 patients who received the combination of sulfonamide and fever therapy, two were cured (11.8 per cent).

During the penicillin period of therapy (1944 to 1947), 44 patients were observed. Of 37 patients who received penicillin, 20 patients were cured (54 per cent). The details of therapy have been discussed with particular reference to daily and total dosage of penicillin, routes of administration, penicillin resistance, duration of therapy, and the causes of treatment failures. A review of the literature containing all of the larger series of reported cases indicates considerable divergence of opinion on these important practical points. These and our own experience, however, lead to certain acceptable conclusions regarding the penicillin treatment of bacterial endocarditis. Adequate daily dosage of penicillin is of paramount importance, and depends to a large extent upon the sensitivity of the organism which may be determined by preliminary *in vitro* studies. If the organism proves sensitive, therapy should begin at not less than 500,000 units of penicillin per day, and if resistant, not less than 1,000,000 units per day. The various technics of administration have not demonstrated any individual superiority. Anti-coagulant therapy has not altered the final therapeutic results and is potentially dangerous. The duration of treatment should extend for at least four to six weeks initially and longer if a relapse occurs.

In spite of chemical and antibiotic therapy, bacterial endocarditis remains a fatal disease in a significant percentage of cases. This group of treatment failures offers a challenge to all students of this disease.

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POLYARTERITIS NODOSA: A CLINICAL AND PATHOLOGICAL STUDY AND REPORT OF SIX CASES *

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POLYARTERITIS nodosa, or periarteritis nodosa as it is frequently designated, is a widespread disease of arteries and less commonly of veins which may occur in any or all of the body structures and results in altered physiology of those organs involved. The clinical manifestations are protean. It is somewhat more common in males in the fourth and fifth decades but is a relatively rare illness and only 350 cases were reported through 1942. Polyarteritis nodosa was first described by Kussmaul and Maier in 1866. However, it has only recently become the object of wide interest and investigation.

From the time of its original description and in the years which followed, etiologic importance was ascribed to a variety of agents. However, none of these has yet been definitely identified with the etiology of this disease. Among the causes suggested have been syphilis, infections, a filterable virus,³⁰ a single unidentified toxic agent, toxic reactions,³¹ diseases of the central nervous system and hypersensitivity.²⁹ It is of interest to note that the etiology of a related disease, lupus erythematosus disseminata, is equally obscure. The similarity of these diseases has been mentioned by Banks⁶ and by Weiss.⁷¹ Klemperer and his associates³⁶ have related diffuse collagen diseases to polyarteritis nodosa, rheumatic fever, scleroderma and disseminated lupus erythematosus. Friedberg and Gross²⁴ reported four patients who at autopsy showed in addition to the expected lesions of polyarteritis nodosa, evidence of rheumatic fever and rheumatic heart disease. The latter was confirmed by the presence of Aschoff bodies in the myocardium. Because of this association they suggested that rheumatic fever was a probable common cause of polyarteritis nodosa. This was also suggested by others.^{21, 24, 49} Gruber²⁸ in 1925, following his experimental induction of the vascular lesions of polyarteritis nodosa in sensitized animals, was the first to suggest that polyarteritis nodosa might be the result of hypersensitivity. Matsugi and Sato⁴⁵ and Vanbel⁶⁸ produced the lesions of polyarteritis nodosa by the injection of horse serum into rabbits, and Harris³⁹ by the injection of macerated material from human cases. Klinge³⁸ Rich and Gregory,⁵⁵ and Selye and Pentz⁶¹ also succeeded in producing poly-

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arteritis in various animals by first sensitizing and then reinjecting them with the same antigen. Numerous materials were utilized including bacteria, horse serum and tissue extracts. Bahrman produced the characteristic arterial lesions in rabbits by repeated large injections of histamine. Clark and Kaplan¹³ reported four patients who received antiserum for pneumonia followed in each instance by fatal serum sickness. At autopsy these patients showed polyarteritis nodosa. These observers did not feel, however, that this was the result of the serum sickness. Eason and Carpenter¹⁸ reported a patient with rheumatic fever who received scarlatinal serum and who at autopsy showed polyarteritis nodosa. They too did not consider that the serum was responsible. On the other hand, Rich⁵⁶ stressed the etiologic importance of hypersensitivity in a report of seven patients treated with sulfonamides who developed serum sickness and eventually polyarteritis nodosa. Later Rich and Gregory⁵⁵ reproduced the lesions of polyarteritis nodosa by the injection of a single large dose of foreign serum in a previously non-sensitized animal. This demonstrated that repeated injections were not necessary for the production of this disease. Selye⁶⁰ by repeatedly administering desoxycorticosterone to rats produced in them the lesions of polyarteritis nodosa, arthritis and myocarditis, the last with Aschoff bodies in the myocardium. In his discussion of the "alarm reaction" he stated that various factors including cold, colchicine, morphine, emotion, trauma and anoxia might cause the release of corticosteroid from the adrenal cortex through the influence of the anterior pituitary corticotropic hormone. The resulting lesions of polyarteritis nodosa and rheumatic fever would be similar to those which developed following repeated injections of desoxycorticosterone in rats.⁶² Wilson and Alexander⁷² have demonstrated the reversibility of the early manifestations of all except the bacterial forms of allergy. The changes become permanent, however, after repeated attacks of asthma, rheumatic fever and other diseases of hypersensitivity. Cohen¹⁴ also has stressed the irreversibility of the vascular changes in polyarteritis nodosa.

It would appear, therefore, from examination of the literature, that the etiology of polyarteritis nodosa is probably diverse and that sensitivity to numerous antigens is an important etiologic cause. There is an additional possibility that psychogenic factors acting through the adrenal cortex may also serve as important causal factors.

PATHOLOGY

Polyarteritis nodosa with its widespread distribution to all parts of the vascular tree can and frequently does involve any organ. The tissues involved in order of their frequency are the kidneys, the heart, the liver, the spleen, the lungs, the mesentery, the peripheral nerves, the skin and the brain.⁴³ Arkin² divided the pathologic lesions into four stages: (1) the stage of degeneration: in this stage there is hyalin degeneration of the media;

(2) the stage of acute inflammation: here the vascular coats become infiltrated with polymorphonuclear leukocytes, eosinophiles, lymphocytes and plasma cells; (3) the stage of granulation: in this stage there is fibroblastic proliferation with partial or total occlusion of the lumen; (4) the stage of healing: the lumen is greatly reduced or obliterated and the wall replaced by scar tissue and periarterial fibrosis.

In this disease any or all stages may be present at the same time. At autopsy frequently the sole lesions are healed.⁷ There are no characteristic findings in the healed stage of polyarteritis nodosa to distinguish it from other forms of arteritis. Gross examination at autopsy may at times show no abnormality and in these cases microscopic examination is required for the diagnosis. The importance of repeated microscopic studies has been stressed by Grant.²⁷ In one of his published cases the diagnosis was not made until repeated serial sections were made.

The degeneration of the media and proliferation of the intima lead to partial or total occlusion of the lumen. This is followed by thrombosis, infarction and eventual fibrosis of the organs involved. There may be aneurysmal dilation with nodule formation along the involved vessels leading to the so-called "peas in a pod" appearance. This is most often seen in the coronary arteries.

CLINICAL MANIFESTATIONS

The Skin. McCall and Pennock⁴⁶ reported skin lesions in 27 of their cases. Included in these manifestations were neurodermatitis, simple erythema, subcutaneous nodules and chronic dermatitis. Ketron³⁶ reported involvement of the skin in 25 per cent of 200 cases. The most common lesions were subcutaneous nodules. Wolff⁷³ reported a case of pulsating nodules. Nodules were also reported in 23 per cent of 177 cases by Harris, Lynch and O'Hare.²⁹ Purpura hemorrhagica accompanying polyarteritis nodosa has been reported,^{33, 17} and the differential diagnosis between this and Henoch's or Schönlein's purpura may be difficult. Thrombosis of the cutaneous arteries may result in ulceration of the skin.³⁵ Other skin manifestations include vesicles, erythema, scarlatiniform eruptions, livido reticularis and urticaria.

Joints and Muscles. Joint pain and myalgia have been noted frequently in the literature.^{46, 33} Joint swellings are also common and migratory arthritis has been reported. Striking muscle pain and soreness are seen and may lead to confusion with trichinosis.⁵⁴

The Nervous System. Gruber²⁸ reported a high incidence of peripheral neuritis and most reported series also confirm this high frequency. (Single nerves are usually involved and this is commonly asymmetrical.⁶⁰) The neuritis is secondary to involvement of the nutrient arteries of the nerves with subsequent ischemia. The paresthesias which result may disappear with improvement in the circulation. Foster and Malamud²² noted neuro-

logic manifestations in 20 of their 300 cases; the most frequently seen were convulsions, meningeal irritations, hemiplegia, cerebellar signs, facial palsy, organic brain syndrome, sluggish pupils, Jacksonian fits and subarachnoid hemorrhage. Polyarteritis nodosa of the retinal vessels⁷ has been reported and the ophthalmologic picture described. The most common neurologic manifestations are motor weakness, particularly foot and wrist drop, paresthesia, muscular atrophy, visual disturbance, headache, vertigo and convulsions.

The Gastrointestinal System. Abdominal pain was reported in 50 per cent of Boyd's 168 cases¹⁰ and epigastric pain in 25 per cent. Anorexia, nausea, vomiting and bloody stools have also been observed. The mesenteric arteries are frequently involved and the resulting thrombosis may result in infarction of the bowel.⁴³ Lamb⁴² and Gruber²⁸ reported thrombosis of the pancreatic artery with hemorrhagic infarction of the pancreas. Chronic pancreatitis was observed in 50 per cent of 12 cases by McCall and Pennock.⁴⁶ They also reported a patient with pernicious vomiting and right lower quadrant rigidity who at autopsy showed thrombosis of the appendiceal artery and a gangrenous appendix. These observers also reported a case of complete thrombosis of the right superior gastric artery. Emerson¹⁹ reported a case of a pulsating mass and murmur in the right upper quadrant due to an aneurysm of the pancreaticoduodenal artery with formation of a retroperitoneal hematoma. Diaz-Rivera and Miller¹⁶ stated that peptic ulcer with hematemesis and perforation was, in their experience, relatively frequent in polyarteritis nodosa and that surgical operations based on mistaken diagnoses were not uncommon. Allen¹ reported similar experiences. Due to mesenteric thrombosis resulting from polyarteritis nodosa, ulcerative enterocolitis with or without bloody diarrhea can result and peritonitis may follow perforation of the bowel wall.^{25, 21, 52} Felsen²⁰ believes that the diagnosis of polyarteritis nodosa may sometimes be made by sigmoidoscopy in those instances where the lower bowel is affected. He stated that the most common findings were hemorrhage, thrombosis and aneurysmal dilatations of the bowel in which the vessels appeared as linear red streaks.

When polyarteritis nodosa involves the vessels of the gastrointestinal tract, the symptoms may mimic peptic ulcer, chronic ulcerative colitis, typhoid fever, cholecystitis, tuberculosis, enteritis and cancer of the stomach or colon. The disease may also resemble acute or subacute surgical conditions such as acute appendicitis, perforated peptic ulcer, acute pancreatitis and acute cholelithiasis.

The Liver. Many patients with polyarteritis nodosa have hepatomegaly. Klotz³⁹ observed two patients with jaundice in whom anatomic examination demonstrated thrombosis of the hepatic arteries, hepatic necrosis and hemorrhage. Another patient had thrombosis of the cholecystic artery, hepatic necrosis and portal fibrosis similar to that encountered in cirrhosis. Other hepatic manifestations include jaundice,⁴⁰ hepatic infarcts and massive subcapsular hemorrhage.⁴⁴ In a study of the causes of hepatic infarction, Pass⁵¹

found that polyarteritis nodosa was the most common cause of this condition. The hepatic symptoms of this disease may simulate cholecystitis, common duct stone or atrophic cirrhosis.

The Endocrine System. Weakness is, perhaps, the most common single complaint of patients with polyarteritis nodosa. The relationship of this complaint to adrenal insufficiency has been suggested by various observers but this has not been proved.⁴⁶ The endocrine organs most frequently involved are the adrenals, pancreas and testes.^{16, 65, 29} A case of diabetes mellitus with polyarteritis nodosa was reported by Middleton and McCarter.⁴⁸ Postmortem examination revealed extensive involvement of the pancreas and its vessels.

The Lungs. Cough, pain in the chest and asthmatic attacks are the most common pulmonary manifestations. However, dyspnea may be secondary either to asthma or heart failure. In 177 cases reported by Harris²⁹ dyspnea was present in 40 per cent, cough in 36 per cent and hemoptysis in 1 per cent. Extensive involvement of the pulmonary arteries and parenchymal infiltration has been reported by Ophuls⁵⁰ and by Hermann.³² The most common pathologic change is the presence of white nodules involving the small pulmonary vessels particularly those in the peribronchial region near the hilum.^{37, 70} Pulmonary fibrosis secondary to infarction may occur and may lead to confusion with tuberculosis.⁴³ Other pulmonary changes encountered include pulmonary infiltration extending out from the hilar area, pneumonitis, small pleural effusions, atelectasis and rarely empyema.⁴⁶ The association of asthma with polyarteritis nodosa was reported by Rackemann and Greene³³ in eight of their own cases and in 27 others collected from the literature. According to these authors the presence of asthma together with numbness of the extremities and eosinophilia of more than 25 per cent indicates the presence of polyarteritis nodosa. This is thought to be particularly true in females. Wilson and Alexander who also studied this relationship found bronchial asthma in 18 per cent of a large group of patients with polyarteritis nodosa.

The Cardiovascular System. The usual cardiac complaints are dyspnea, palpitation, precordial pain, cough and angina pectoris. The more common findings are hypertension, tachycardia, systolic murmurs and peripheral edema. Cardiac enlargement or pericardial effusion may also be present. The endocardium may be involved by nodule formation or inflammatory thickening.^{31, 70} Friedberg and Gross²⁴ reported four patients with the clinical picture of rheumatic fever who had rheumatic valvular and myocardial lesions together with the characteristic vascular changes of polyarteritis nodosa. Although it has been reported²⁷ myocardial infarction is rare. The infrequency is explained on the basis that the coronary changes occur slowly with ample time for the development of collateral vessels.⁴⁵ Hypertension is relatively common and was found in 53 per cent of one series of 177 cases.²⁹ Cardiac enlargement usually takes place terminally in those cases with hyper-

tension and congestive failure. However, enlargement is said to occur with chronic coronary insufficiency in the absence of hypertension.

Subcutaneous nodules often occur along the course of some of the small superficial arteries. The superficial temporal artery may be so involved but more commonly temporal arteritis is unassociated with polyarteritis nodosa.⁴³ Thrombosis of the central retinal artery,⁶ bilateral optic atrophy and transient amaurosis have all been recorded. Pericardial tamponade has been noted following rupture of a coronary artery aneurysm.⁶⁷ Vein involvement in periarteritis nodosa is also encountered.¹⁶

The Genito-Urinary System. Polyarteritis nodosa of the kidney is common and was found in 80 per cent of his reported cases by Baker.⁴ Nocturia, hematuria, cylindruria, hypertension and edema were all observed. At times the findings simulated those of acute nephritis. All of Spiegel's cases who came to autopsy had renal findings.⁶⁶ The lesions of malignant nephrosclerosis and of chronic glomerulonephritis were occasionally encountered. It was suggested that the vascular reactions of these kindred diseases might be the result of a similar noxious agent. This is of interest in the light of Selye's recent work in the production of the lesions of polyarteritis nodosa and nephrosclerosis in animals following repeated administration of adrenal cortical extract.⁶²

Moderate hypertension occurs in most cases as a late manifestation. However, some cases are indistinguishable clinically from malignant hypertension.³⁴ Nitrogen retention occurs in many instances and clinical uremia was observed in 13 per cent of one group of 177 cases.²⁹

Collapse and death following rupture of aneurysms of the interlobular arteries with formation of large perirenal hematomas were observed in 18 cases by Boyd.⁸ The roentgen-ray shadow of such a mass has been mistaken for renal tumor.⁵⁸ Renal hemorrhage may simulate essential hematuria or suggest the presence of stone or tumor.

The arteries of the testicles and epididymis are not uncommonly involved and may give rise to localized pain and swelling in this region. Orchitis due to infarction is a rare complication. Scrotal pain has been reported.²⁴

LABORATORY FINDINGS

It is usual to find a moderate leukocytosis ranging between 10,000 and 25,000. However, counts of 60,000 have been reported. There is usually a shift to the left in the white blood cells. Eosinophilia is inconstant. Various reports place the incidence of eosinophilia at from 20 to 33 per cent. In a large group of cases collected from the literature Wilson and Alexander⁷² found that when bronchial asthma and polyarteritis nodosa coexisted all but 3 of 47 such cases demonstrated eosinophilia above 11 per cent with an average for the group of 53.5 per cent. By contrast, only 9 of 151 cases of polyarteritis nodosa without bronchial asthma had eosinophilia above 6 per cent. It is probable that increasing eosinophilia is related to activity.

Blood eosinophile counts as high as 84 per cent have been reported.⁵² The sedimentation rate is commonly increased. Abnormal urinary excretion and nitrogen retention are frequently present. Hyposthenuria is encountered.

A positive Wassermann reaction or other serologic test for syphilis is encountered on occasion. In the past this has given rise to the suspicion that syphilis may play a part in the etiology. Such positive tests are frequently biologic false positives with low titers and subsequently return to normal. It has been observed that these patients tolerate transfusions poorly and it has been suggested that atypical agglutinins may be responsible for this as well as for the abnormal serologic reaction.⁴³

THE RADIOLOGIC EXAMINATION

The roentgen-ray examination is reported by some observers to be of little assistance,⁴⁵ however, in some instances it has proved of considerable importance. The fan-like pulmonary infiltration extending out from the hilar regions although not diagnostic of polyarteritis nodosa may suggest that diagnosis in an otherwise obscure problem.

THE ELECTROCARDIOGRAM

The electrocardiogram is of considerable importance and at times may be the only indication of coronary artery involvement. There may be tachycardia, flattening or inversion of the T waves, and evidence of left heart strain. Polyarteritis nodosa, however, does not produce a characteristic electrocardiographic pattern.

MICROSCOPIC EXAMINATION

The most important laboratory aid in the diagnosis of polyarteritis nodosa is biopsy of subcutaneous nodules or, in their absence, of skeletal muscle. One should be aware of the fact, however, that a single negative biopsy does not rule out the diagnosis of polyarteritis nodosa. Repeated microscopic examinations are indicated in suspected cases.

The incidence of symptoms and findings in polyarteritis nodosa is well summarized in the following table modified from Harris, Lynch and O'Hare.²⁹ This was obtained from a review of 177 cases.

Fever	81%	Vomiting	33%
Leukocytosis	73	Eosinophilia 4%	33
Albuminuria	65	Purpura or petechiae	27
Abdominal pain	56	Headache	26
Hypertension	53	Visual disturbance	23
Edema	49	Nodules	23
Neuritis	49	Allergy	21
Hematuria	48	Muscle atrophy	20
Weakness	45	Cyanosis	20
Weight loss	44	Icterus	17
Dyspnea	40	Convulsions	12
Cough	36	Positive serology	11
Sensory involvement	34	Vertigo	8
Arthritis	34	Other significant manifestations	5

In 76 other cases reviewed by the same authors the following was noted:

Anemia	48	Hematuria or melena	13
Tachycardia	48	Adenopathy	11
CNS involvement	26	Chills	8
Muscle soreness	26	Diarrhea	6
Coma	21	Hemoptysis	1
Uremia	13		

PROGRESS AND TREATMENT

The more acute cases of polyarteritis nodosa commonly encountered go on to total debility and death in a period of from a few weeks to several months. However, the disease may be punctuated by periods of remission and exacerbation and some patients survive for several years. An occasional case appears to recover. Cures are thought to occur in those instances where progressive changes cease before the vital organs have been too extensively involved. This may actually take place in from 5 to 10 per cent of the cases. It may be more frequent, however, since some of the milder cases fail to be diagnosed and classified. It is of interest to note that only three of Grant's seven reported cases had died after three years.²⁷ The usual modes of death are congestive heart failure, uremia and cerebral hemorrhage.

There is no effective therapy for polyarteritis nodosa. In all instances treatment is purely symptomatic and supportive. It includes such measures as proper diet, sedation, mechanical support for painful muscles and joints, transfusions, digitalis for cardiac failure and antibiotics for intercurrent infections. In view of the fact that sulfonamides have been suspected as etiologic agents, they should not be employed. Probably they should not be used in any event except where the indications are unmistakable. The current use of potent and possibly allergenic drugs without clear indications may well be responsible for some of the diseases of obscure origin including those related to hypersensitivity.

CASE REPORTS

During a single 12-month period at the Veterans Administration Hospital, West Roxbury, Massachusetts, six cases of polyarteritis nodosa were encountered. Of these one is still alive but showing signs of activity while five have died. Pathologic examinations were made on all. Although the cases differed from each other in symptomatology and in the primary system involved, they collectively demonstrated most of the clinical features and pathological findings of polyarteritis nodosa and possibly one hitherto undescribed manifestation.

Case 1. A 26 year old white male shoe worker was hospitalized for the first time on June 19, 1946 complaining of pains in the arms and legs of six months' duration. He was well until 1943 when, while in Iceland, he developed upper abdominal pain and was found to have a peptic ulcer. In January 1946 he began to have pain and tenseness in the calf muscles of the left leg which gradually extended to the ankles and shortly to the left upper arm. In April of the same year similar symptoms were

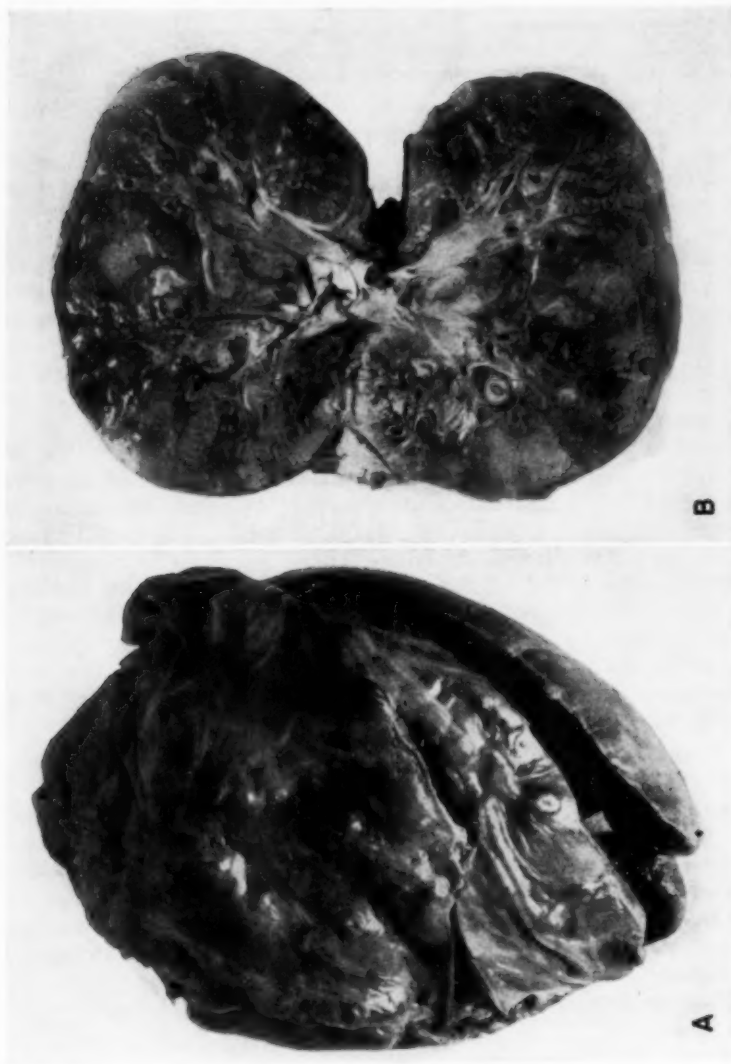


FIG. 1. *Case 4.* Heart and kidney. There are nodules and small aneurysms in the coronary arteries. The kidney shows aneurysms and small pale infarctions.

noted in the right leg and arm. This became so severe that he had to give up working and was admitted to another hospital. At this time physical examination revealed a well developed and nourished young white man who was acutely ill. There was marked tenderness and slight muscle spasm in the right upper quadrant and a curious firmness of the calves of both legs. Homan's sign was positive bilaterally. The blood pressure was 112/56 mm. Hg, the white blood count was 14,800 with 4 per cent eosinophiles. All other examinations were negative. A biopsy of the left calf showed chronic inflammatory reaction with eosinophilic infiltration. No parasites were seen.



FIG. 2. Case 4. Mesentery and jejunum. There are nodules along the mesenteric vessels peripherally. (The larger masses are lymph nodes.)

The pathologic diagnosis was chronic myositis. Subsequently the patient was transferred to this hospital where additional history revealed that he had lost 30 pounds in six months. The peptic ulcer was asymptomatic. Examination revealed a young white man who showed evidence of weight loss. There was a brown pigmentation of the skin over both ankles and legs. Many fine and coarse râles were heard throughout both lungs. There was a right lower quadrant abdominal scar and slight tenderness in the right upper quadrant. There was atrophy of the left triceps and the calf muscles of both legs with a "porky" feeling to these muscles. The red blood count was 4.6M, white blood count 12,500 with 52 per cent polymorphonuclears, 30 per cent lymphocytes, 14 per cent monocytes and 4 per cent eosinophiles. The urine was negative. The serum calcium was 12 mg. per cent. The blood serologic test for syphilis and spinal fluid examinations were negative. The 24-hour creatin excretion was 288 mg. (normal value 0 to 196 mg.). The alkaline phosphatase was 1.4 Bodansky units. The sedimentation rate was 4 mm. per hour and the serum proteins were normal. The stools demonstrated the presence of occult blood and a gastrointestinal series showed a benign duodenal ulcer. The radiographs of the bones showed slight to marked atrophy in the region of the knees. A Brucellin skin test was strongly positive. A muscle biopsy of the right gastrocnemius muscle was essentially negative but showed a scanty lymphocytic perivascular infiltration. However, in July 1946 a muscle and skin biopsy of the left forearm showed evidence of subacute polyarteritis nodosa.

During the first two months of hospitalization the temperature was elevated to 100°. This subsequently subsided. Various types of therapy including quinine, multiple vitamins, testosterone and penicillin were employed without benefit. The pain in the forearms was frequently severe. Eventually, however, this subsided. From time to time small subcutaneous nodules appeared along the ulnar surface of the right arm. On occasion a positive Babinski sign was noted on the right side. Gradually, as the pain diminished the patient began to regain his strength and was able to begin walking. In September he was permitted to go home although at this time fresh subcutaneous nodules were seen. The following month the patient's weight had increased and he felt better. He was able to walk increasing distances each day although the sedimentation rate was persistently elevated and subcutaneous nodules recurred from time

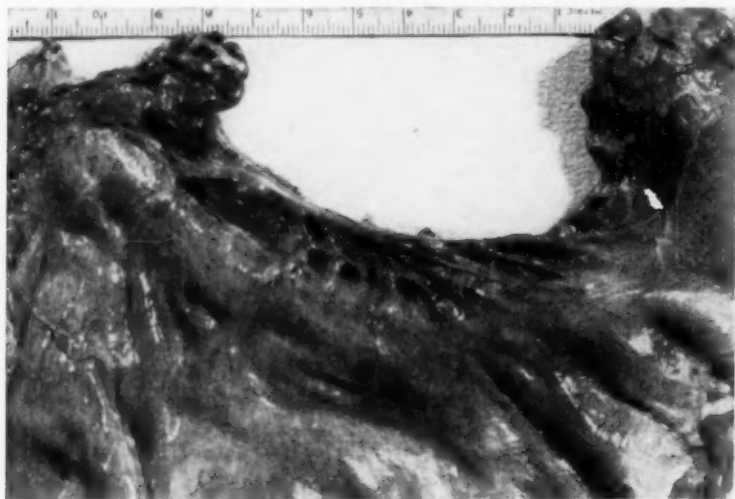


FIG. 3. Case 4. Stomach. Nodules on the vessels of the lesser curvature.

to time. The patient attempted to return to work in the spring of 1947 but was unable to do this. When last seen (January, 1948) he was walking well and had done some work. However, he tired easily and the calf muscles still retained a trace of the firmness originally noted on admission.

Comment: There are several points of interest in this patient worthy of additional attention. The most persistent and troublesome complaints were largely limited to the skeletal muscles. This suggested various diagnostic possibilities including trichinosis and various myopathies of obscure origin. The first two muscle biopsies did nothing to clarify the problem. The third, however, turned out to be diagnostic. A peptic ulcer was present in this patient prior to and during the course of his observed illness. Its relationship to the associated polyarteritis nodosa is unknown and conjectural. In a similar manner there was no demonstrated connection between the positive agglutination test to brucella and the underlying illness.



FIG. 4. A. Case 6. Heart. Wall of the left auricle showing Aschoff nodule with large central area of necrotic collagen. B. Case 2. Appendix. Striking lesion in the submucosa from which the diagnosis was first made.

Case 2. A 51 year old white machinist entered the hospital on February 2, 1946 with the complaint of severe epigastric pain. There was an 18 year history of duodenal ulcer. In spite of diet and the use of antacids the typical post-prandial pain increased during periods of stress. There had never been any bleeding. Two hours before admission he developed a sudden severe sharp epigastric pain and vomited. Examination revealed a well developed white man who looked acutely and chronically ill. The head, neck, eyes, nose and throat were all negative. There were coarse sibilant râles close to the midline but the lungs were otherwise normal. The heart was normal. Blood pressure was 90/70. The abdomen was rigid throughout but no masses were felt. The examination was otherwise normal. The hemoglobin was 94 per cent and the white blood count 8,300. The blood serologic test for syphilis was negative. Immediate surgery was performed and a perforation on the lesser curvature of the stomach was identified and sutured.

Postoperatively the patient continued to complain of gnawing epigastric pain. There was a highly acid night gastric secretion of 1 to 2 liters. Radiography demonstrated a constant deformity of the duodenum and hyperperistalsis of the stomach. Because of persistent symptoms an abdominal vagectomy and posterior gastroenterostomy was performed on April 19, 1946. After a brief period of comparative comfort the patient began to run a low grade fever and complained of headaches, muscle pains and weakness. At this time sulfadiazine was started in doses of 1 gram every four hours for seven days. Sodium bicarbonate was given with each dose. Examination at this time was negative except for moderate pallor and slight edema of the ankles. There was also some slight right upper quadrant tenderness. The heart and lungs were normal, white blood count was 14,000 with 80 per cent polymorphonuclear leukocytes and 1 per cent eosinophiles. Extensive studies were made in an attempt to localize the process responsible for the fever and symptoms. These included roentgen-rays, blood cultures and agglutinations. However, except for the radiographic demonstration of a slightly high diaphragm on the right side all the examinations were negative. Accordingly, on June 25, an exploratory laparotomy was performed but no abscess was demonstrated. The operative findings were all negative with the exception of a somewhat enlarged spleen. The appendix was removed and this on microscopic examination revealed the presence of polyarteritis nodosa.

From the time of the last operation until his death in January 1947, the patient went first gradually then rapidly downward. He complained of severe pounding headaches which occurred chiefly at night, generalized abdominal pain, nausea and weakness. Striking weight loss occurred. During the summer and fall of 1946 subcutaneous nodules appeared and subsided. The blood pressure which earlier had been 120/78 gradually increased to 170/120. In December 1946 retinal hemorrhages appeared and resulted in blindness of one eye. During the same month dyspnea which had previously been slight became severe and occurred in paroxysms. This improved somewhat following the administration of digitalis. Bloody sputum was also noted and a roentgenogram of the chest revealed a striking fan-shaped infiltration of the hilar regions of both lungs.

The urine which was normal originally subsequently demonstrated a fixed specific gravity of 1.008, 1 to 3 plus albumin, hyalin casts and red blood cells. Phenolsulfalein excretion of 76 per cent in May 1946 diminished to 8 per cent in November. The white blood count ranged from 8,300 to 13,700 with from 74 to 90 per cent polymorphonuclears and never more than 3 per cent eosinophiles. The hemoglobin diminished from 15 to 10.2 grams and the red blood count from 4.9M to 3.6M. The sedimentation rate was always elevated and averaged 25 mm. per hour. The icteric index was normal. Occult blood tests on the stools were positive on all occasions. During the last three days of his life the patient complained bitterly of pain. He became disoriented, then semi-comatose and died on January 15, 1947.

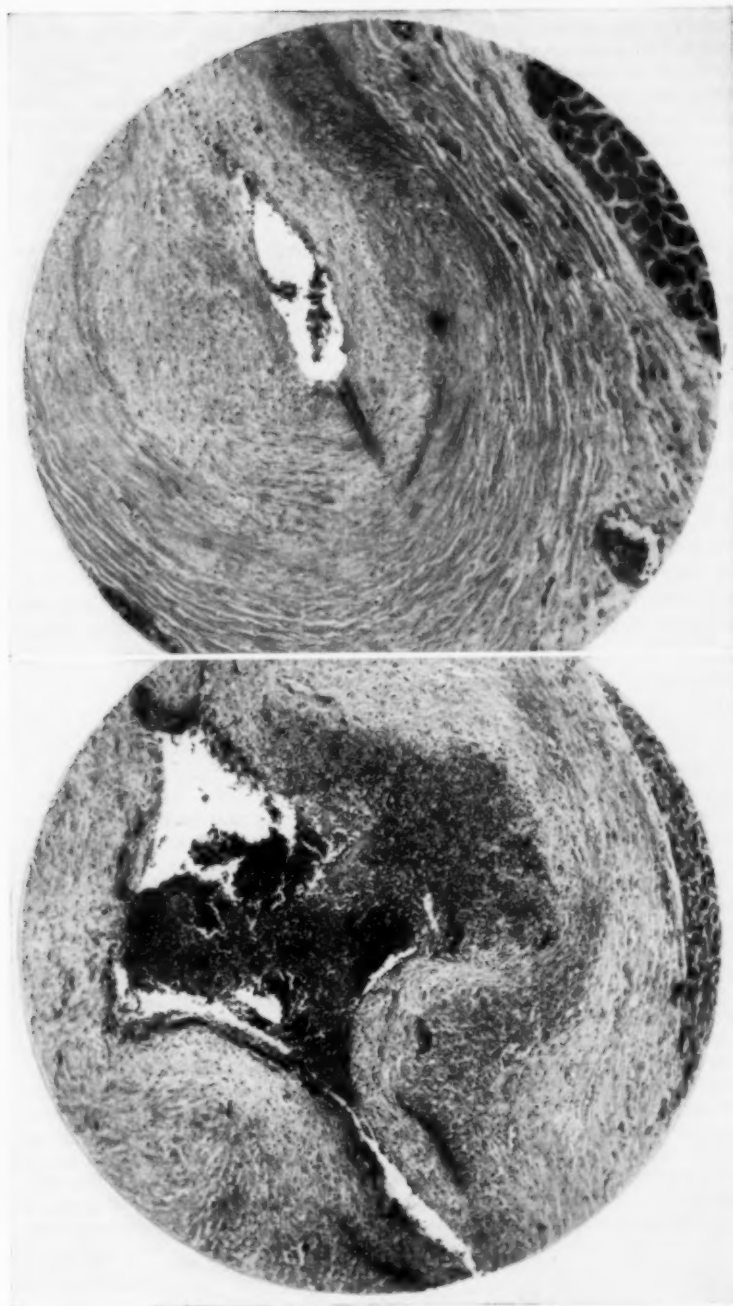


FIG. 5. Case 4. Small coronary artery branches. A. Aneurysmal dilatation and recurrent fibrinoid necrosis. B. Old medial and peripheral fibrosis. Old thrombosis.

At autopsy this patient showed evidence of generalized but healed polyarteritis nodosa with little evidence of recurrent acute lesions. Among the organs involved were the heart, bronchi, spleen, esophagus, mesentery, ileum, pancreas, adrenal capsule, kidneys and testicles. There were miliary infarcts of the myocardium. There was evidence of old bilateral pyelonephritis. There was an extensive membranous gastroenterocolitis which was attributed to inadequate blood supply and a terminal *E. coli* septicemia with generalized fibropurulent peritonitis. There was pleural and pericardial infection with the same organism. There was hyperplasia of the adrenal cortex.

Comment: The diagnosis of polyarteritis nodosa was made in this patient almost wholly by chance and resulted from the microscopic examination of the appendix which was removed during the course of an exploratory laparotomy. Until this occurred the patient presented a fascinating and apparently insoluble problem in diagnosis. It is not plain whether the peptic ulcer which had been present for many years prior to the final illness was at all related to it. However, the high incidence of organic gastric disease in polyarteritis nodosa cannot be overlooked. Another possibly related factor in this patient was the history of sulfonamide therapy following one of his operations. After the last operation the disease progressed along classical lines with involvement of the skin, lungs, kidneys and heart. Nitrogen retention followed earlier evidence of nephritis and this was associated with hypertension, angina and finally cardiac failure. Of further interest in this case was the electrocardiogram which, though normal originally, later showed the changes of left heart strain and hypertrophy. In view of Selye's demonstrations the adrenocortical hyperplasia in this patient may have been more than a coincidence.

Case 3. A 40 year old white male clerk was admitted to the hospital on July 23, 1946 with a history of abdominal pain of five weeks' duration. This consisted of generalized abdominal cramps which radiated to both flanks and which lasted for about five minutes each time. These occurred every four or five hours, were worse after meals and early in the illness awakened him from sleep. He was examined by a local physician who treated him with sulfadiazine. Following this he vomited on several occasions. Striking anorexia occurred and for three weeks prior to admission the patient took only liquids. Constipation occurred, the stools became tan colored and the urine dark. Just prior to admission the pains began to radiate to both testicles. There were frontal headaches, pains and stiffness in the ankles and fingers and a low grade fever.

The patient had had rheumatic fever at the age of seven and again at 14, pleurisy at the age of 20, and pneumonia 15 years later. Until the age of 13 he had frequent middle ear infections and subsequent slight deafness. He was a moderate drinker.

Examination revealed a well developed but poorly nourished white man who was acutely ill. The temperature was 102°, the pulse 100 and the respirations 20. There was a moderate tremor of the hands. The skin was dry, scaly and revealed small stellate telangiectases over the abdomen and lower chest. It was otherwise negative. There was no lymphadenopathy. The tongue was furred, the teeth poor and pyorrhea was present. The heart was not enlarged, a soft systolic murmur was heard at the apex and a very soft diastolic blow was noted along the left sternal border. The belly was slightly distended, soft and non-tender. The liver was non-tender and could be felt three fingers below the right costal margin. The spleen was enlarged to percus-

sion. There was a 2 mm. firm and rather tender nodule in the right epididymis. Slight pitting edema was noted over the ankles and feet. The examination was otherwise negative.

The red blood count was 4.2M, hemoglobin 13 grams, white blood count 16,350 with 84 per cent polymorphonuclears, 12 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophiles. The urine contained 2 plus albumin, a few red blood cells and an occasional white blood cell. The serum proteins were normal, serum bilirubin .3 mg., and non-protein nitrogen 32 per cent. The urinary urobilinogen was positive in 1:80 dilution. The stools showed 2 plus occult blood. Several blood cultures were negative. Agglutinations for typhoid, paratyphoid A and heterophile determinations were all negative. Agglutination to paratyphoid B was positive in a dilution of 1:200.

Roentgenograms of the chest and abdomen were negative. A barium enema was negative. An electrocardiogram showed low to diphasic T waves in all the limb leads. The chest leads, however, were negative. It was interpreted as suggesting myocardial disease, type not apparent.

The hospital course was characterized by fever which rose to 101° daily, cramping abdominal pains and almost complete loss of appetite. Nutrition was maintained by the intravenous administration of glucose and amino acids. Eight days after admission while attempting to get into bed the patient gasped, suddenly became cyanotic and died.

At autopsy there were typical lesions of polyarteritis nodosa in the acute, sub-acute and healing stages in the heart, lungs, spleen, pancreas, stomach, intestine, liver, kidney, adrenal, prostate and epididymis. There were small infarcts of the myocardium, the liver, kidneys and adrenals. There was a small, probably agonal ulcer of the stomach. There was extensive involvement of the pancreas with numerous small to medium infarcts, many showing autodigestion. There was slight aortic stenosis thought to be of rheumatic origin. Minute fenestrations of the aortic cusps were present and served to explain the diastolic murmur heard on examination.

Comment: The diagnosis in this case was not made ante mortem and not actually confirmed until after microscopic study. In spite of this, extensive changes were present in most of the vital organs.

Case 4. A 23 year old Negro student was admitted on November 29, 1946 complaining of periumbilical pain. In 1944 while serving in the Pacific area the patient developed a fever of unknown nature which lasted for one week. Following this he had headache, lumbar pain and nervousness for which he eventually received a medical discharge. In the following year most of his complaints cleared with the exception of a backache. However, this too became milder and tended to diminish following activity. On arising on the morning of October 10, 1946 the patient for the first time became aware of a persistent pain in the periumbilical region. There were fever, nausea and vomiting. The appetite, however, was not impaired and there were no other symptoms. There was a history of gonorrhea in 1939 when the patient was 15. The history was not otherwise contributory.

Physical examination revealed an acutely ill young Negro with a fever (103°) which appeared out of proportion to the degree of illness. The head, eyes, ears, nose and throat were normal. The tongue was coated. The neck and chest were negative and the lungs were clear. The heart was normal. The blood pressure was 120/80. The abdomen was negative except for slight tenderness around the umbilicus. There was slight generalized lymph node enlargement. The remainder of the examination was entirely normal.

On admission the red blood count was 3.5M, with 10.9 grams of hemoglobin. The white blood count was 16,500 with 79 per cent polymorphonuclears, 13 per cent lymphocytes, 5 per cent monocytes and 3 per cent eosinophiles. The urinalysis was normal. The serology was positive. A roentgen-ray film of the chest was negative.

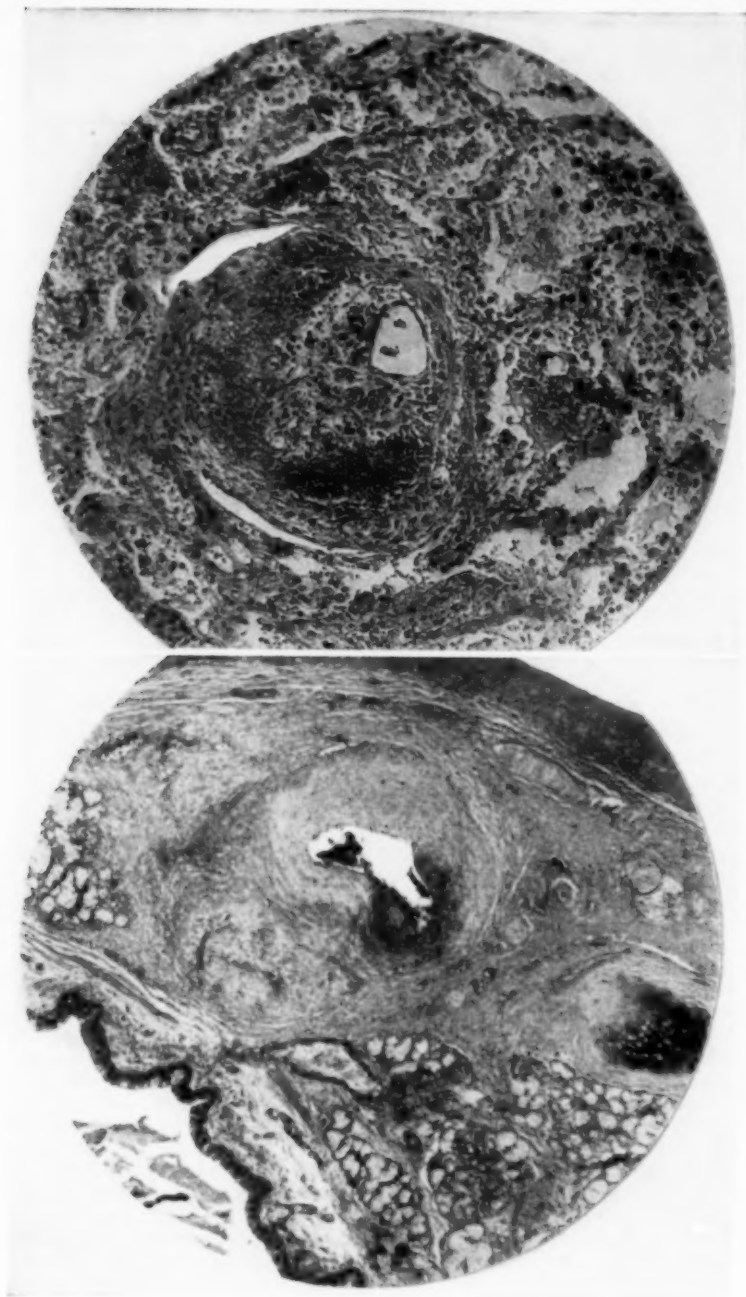


FIG. 6. A. Case 4. Bronchial artery. There is dilatation, marked fibrosis, thickening of the wall and necrosis of much of the original wall.
B. Case 6. Pulmonary vessel. There is a concentric zone of necrosis in the wall and organizing exudate in a few adjoining alveoli.

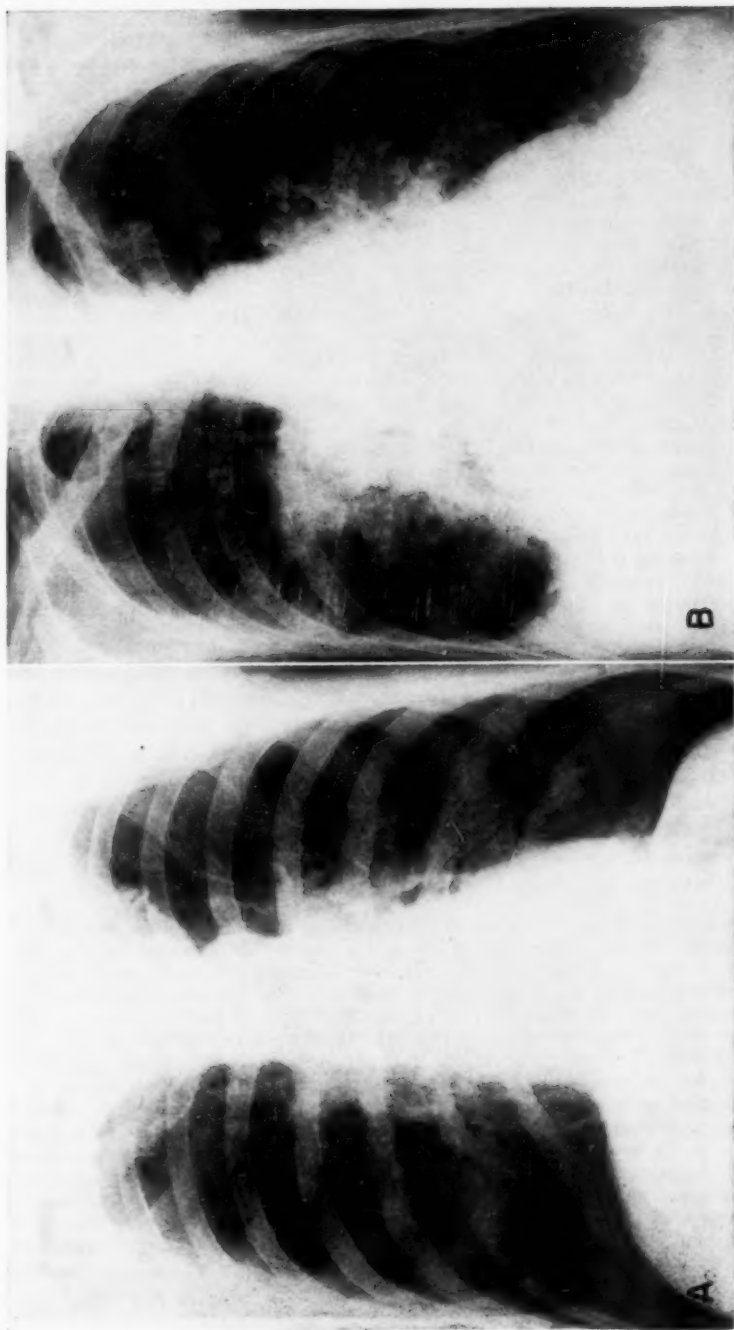


FIG. 7. Case 2. Roentgenograms of the chest. A. Early in the illness. B. Late in the course of the disease showing striking perihilar changes, cardiac enlargement and fluid at both bases.

The patient ran a spiking temperature which rose to 102°-103° daily for the first two weeks. However, in spite of this fever he did not appear seriously ill. The abdominal pain was inconstant and a soft systolic murmur appeared at the apex. Blood cultures obtained early in the illness were negative and a tuberculin test was also negative. A muscle biopsy was obtained and showed no evidence of polyarteritis nodosa. Agglutinations for typhoid, paratyphoid, brucella and tularemia were all negative.

Beginning during the third week and from then until his death the patient began to have severe, constant, nonradiating pain and tenderness which was maximal above and just to the right of the umbilicus. A serum amylase at this time was 40 units. The urine which had been normal began to show 1 to 3 plus albumin, hyalin casts, red and white blood cells.

For a period of one week during the middle of the illness the temperature came down to normal. During this interval extensive x-ray studies of the gastrointestinal tract were made and found to be normal. The red blood count remained at 3.2M, and the white blood count varied between 18,000 and 24,000 with 85 per cent polymorphonuclears, 11 per cent lymphocytes, 1 per cent monocytes and 3 per cent eosinophiles. A sternal marrow was normal and blood studies for sickling were negative. The blood pressure gradually rose to 185/140 mm. Hg. On the morning of November 26 the patient began to have repeated epileptiform convulsions with intervals of deep sleep between seizures. He became stuporous and could not be roused. A lumbar tap revealed grossly bloody spinal fluid. He died later the same evening.

Anatomic examination revealed healed and recurrent acute lesions of polyarteritis nodosa involving the vessels of the heart, lungs, spleen, stomach, mesentery, intestine, gall bladder, pancreas, testes, epididymis, the internal mammary arteries, celiac axis, gastric arteries, etc. There were miliary infarcts of the myocardium, spleen and kidney. There was a large, fresh cerebral hemorrhage on the left side.

Comment: This case was one with widespread arterial involvement and a rapid fatal course. In spite of extensive changes in most of the organs the symptoms were largely confined to the gastrointestinal tract and terminally, due to the cerebral hemorrhage, to the central nervous system. Although the correct diagnosis remained unsuspected for some time, it became apparent before death when the renal findings and hypertension appeared; this in spite of a negative muscle biopsy. The serologic test for syphilis in this patient was positive during life. However, at autopsy there were no lesions of syphilis. There was no definite history of sulfonamide ingestion in this case.

Case 5. A 56 year old white building inspector was well until January 1, 1947 when he first became aware of fatigability and weakness. In March of the same year he had an acute respiratory infection. He then developed pain in the calves of both legs and a vein ligation was performed at another hospital for deep thrombophlebitis. At the same time a low grade afternoon temperature appeared and the patient received 8 grams of sulfadiazine over a two day period. He also received 500,000 units of penicillin daily for six days. However, the fever persisted and the patient was admitted to this hospital on April 5, 1947. The past history was not otherwise contributory.

Physical examination revealed a well developed and nourished, alert and well oriented white man. There was some narrowing of the retinal arterioles. There was dullness at the base of the right lung and the breath sounds were bronchovesicular over the same area. The blood pressure was 200/106 mm. Hg. The heart was somewhat enlarged to percussion and there was a Grade II systolic murmur at the apex. The liver was slightly enlarged. The prostate was symmetrically enlarged. Well healed vein ligation scars were present. Moderately firm 2 by 2 cm. lymph nodes were noted in the left axilla.

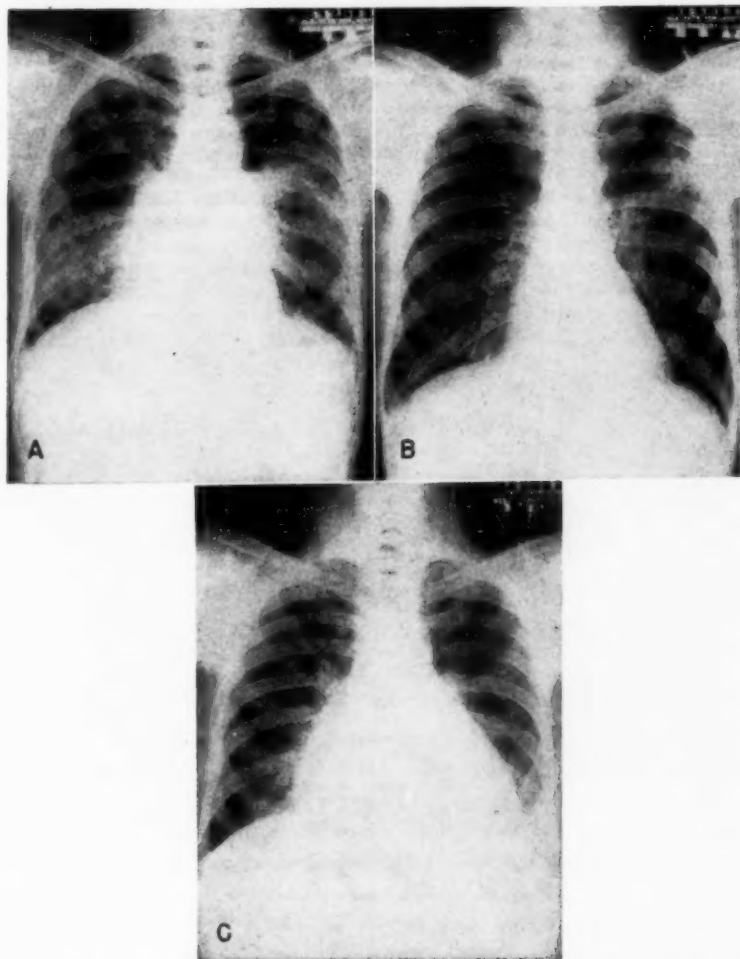


FIG. 8. Case 6. Roentgenograms of the chest. A. Extensive pulmonary infiltration extending fan-like from the hilar areas. B. Three months later. Extensive improvement. C. Pericardial effusion, fluid at the left base.

The red blood count was 4M, hemoglobin 10.8 grams, white blood count 25,600 with 90 per cent polymorphonuclears, 7 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophiles. The urine was negative. An x-ray of the chest showed slight transverse enlargement of the heart. The lungs were clear. A flat film of the abdomen was negative. A skull film showed thickening and granularity of the vault with multiple small circumscribed areas of radiolucence measuring 5 to 10 mm. in diameter. The general appearance of the bones resembled that occasionally seen in systemic disease.

The patient was febrile during his entire hospital admission with the temperature varying between 99° and 102°. The pulse was 88 to 120. Shortly after admission the patient became incontinent of urine and feces. Two blood cultures were reported positive for pneumococci. He became mentally slow and at intervals unresponsive and disoriented. At other times he was relatively alert. The tongue became beefy red and papilledema of the discs was noted. The ankle jerks disappeared bilaterally and the left knee jerk diminished. There was evidence of poor coordination and diminished position sense.

The red blood count varied between 3.6 and 3.8M. The white blood count was elevated to between 15,400 and 28,200 with from 79 to 90 per cent polymorphonuclears. The eosinophile count was between 1 and 6 per cent. The urines were normal until one week prior to death when they began to show albumin, sugar, hyalin casts, red cells and numerous bacteria. The specific gravity varied between 1.010 and 1.018. Blood chemistry studies were essentially normal with the exception of the serum proteins which showed a reversal of the A:G ratio. The serologic test for syphilis was negative. The stools showed 4 plus occult blood on two occasions. The sedimentation rate was persistently elevated to 50 mm. or more per hour. Spinal fluid sugar and proteins were elevated.

Because of the positive blood cultures and the presence of a soft systolic murmur a diagnosis of bacterial endocarditis was entertained and the patient was treated with large doses of penicillin for a period of one month. However, there was a total lack of response. A muscle biopsy was performed and following this, the patient became semi-comatose and began to show evidence of left facial flattening and ptosis. Progressive emaciation was noted and dysphagia occurred. The temperature and pulse gradually rose, an apical diastolic gallop developed terminally and the patient died quietly on May 30, 1947.

[illegible]

The findings at autopsy were those of polyarteritis nodosa superimposed upon generalized arteriosclerosis. There was no evidence of bacterial endocarditis. There was an old, large cerebellar infarction with widespread focal encephalomalacia and status cribrosus. There were lesions in the vessels of the heart, bronchi, lungs, duodenum, mesentery, colon, spleen, liver, pancreas, kidney, spermatic cord, adrenal capsule and aortic adventitia. Some of the lesions, particularly in the adrenal capsule, aortic adventitia and spleen, suggested the arteriolar necrosis of malignant hypertension. The changes in the larger vessels were more characteristic of polyarteritis nodosa with extensive necrosis, fibrosis and leukocytic infiltration. There were multiple renal infarcts.

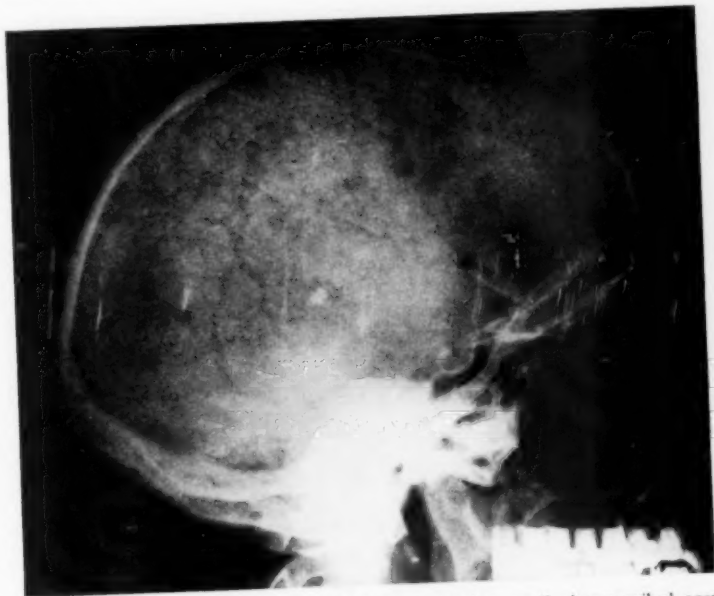


FIG. 9. Case 5. Roentgenogram of the skull demonstrating small circumscribed areas of radiolucence associated with thickening and granularity of the vault.

The skull which had a curious appearance by x-ray showed on microscopic section wide trabeculae with mosaic development and prominent cement lines. The arterioles showed no evidence of polyarteritis nodosa. The findings suggested old Paget's disease. However, although evidence of destruction was present, proliferation was not observed. The association of these osseous changes with the coincident polyarteritis nodosa remains unproved and conjectural.

Comment: The correct diagnosis in this case was at all times obscure. The symptoms were largely indicative of lesions of the central nervous system and these together with the fever, positive blood cultures and valvular murmurs suggested the diagnosis of bacterial endocarditis. The hypertension antedated and was probably not etiologically related to the associated polyarteritis nodosa.

Case 6. A 38 year old white postman was admitted to the hospital on February 3, 1947 with the complaint of asthma. He had been perfectly well until June 1945 when he acquired a non-productive cough, itching of the eyes and coryza. The following year he developed definite bronchial asthma which was unsuccessfully treated with desensitization injections. One month before admission the patient became aware of anorexia and a 15 pound loss of weight. At the same time he became troubled by gnawing epigastric pains which occurred between meals and were relieved by milk and other foods. A pain also appeared in the left chest which was made worse on coughing. The past history was not otherwise remarkable and the family history was noncontributory.

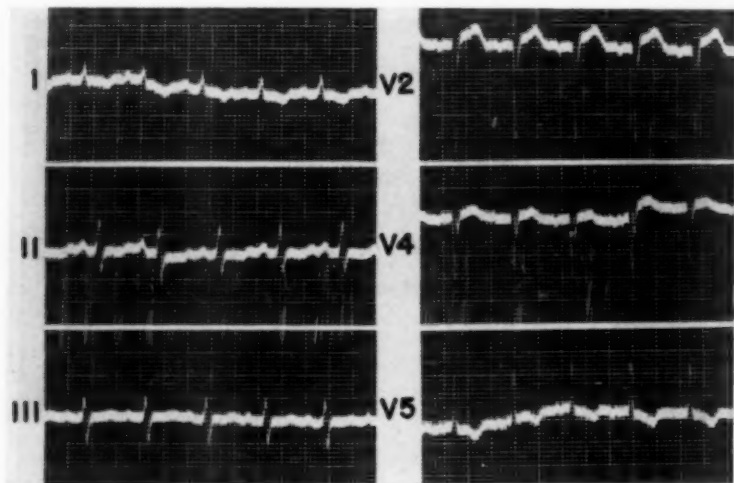


FIG. 10. *Case 6.* Electrocardiogram obtained during presence of pericardial effusion.

Physical examination on admission disclosed an acutely ill, thin white man. There were characteristic inspiratory and expiratory wheezes throughout both chests and moist râles at the right base. The heart was normal, blood pressure was 120/80 mm. Hg. The liver and spleen were not felt and the abdomen was entirely negative. The examination was otherwise normal. The white blood count was 22,100 with 38 per cent eosinophiles. The red blood count was 4.35M, and the hemoglobin was 13 grams. The urine was negative. The x-ray showed extensive infiltration of both lungs extending from the hilar areas toward the periphery with slightly greater density in the lower lung fields. This was felt to be consistent with either atypical pneumonia, Löeffler's syndrome or tuberculosis. A gastrointestinal series showed a delay in emptying of the duodenum at the junction of the descending and ascending loops but no peptic ulcer could be demonstrated.

The patient remained in the hospital continuously until his death on September 20, 1947, a period of over seven months. Throughout his hospitalization he ran a low grade fever. There were consistent and striking variations in the appearance of the lungs by x-ray. The pulmonary infiltration diminished in some locations and increased in others. On two occasions, coincident with increased pulmonary findings and signs the fever became greater than formerly. Both times improvement followed the administration of penicillin. He developed a marked pericardial effusion which

receded but reappeared just before death. This was tapped on two occasions and clear straw-colored fluid was obtained. Electrocardiographic changes were noted which were felt to be consistent with myocarditis or pericarditis. Treatment was at all times asymptomatic and directed to the pulmonary and cardiovascular systems. Several muscle biopsies were performed and one showed focal perivascular infiltration suggesting trichinosis.

Throughout the hospitalization the white blood count ranged between 11,000 and 20,000 with eosinophilia as high as 82 per cent. The sputum showed no organisms or fungi but did demonstrate a 95 per cent eosinophile count. The red blood count varied between 3,000,000 and 4,000,000 and the hemoglobin between 10 and 12 grams. The

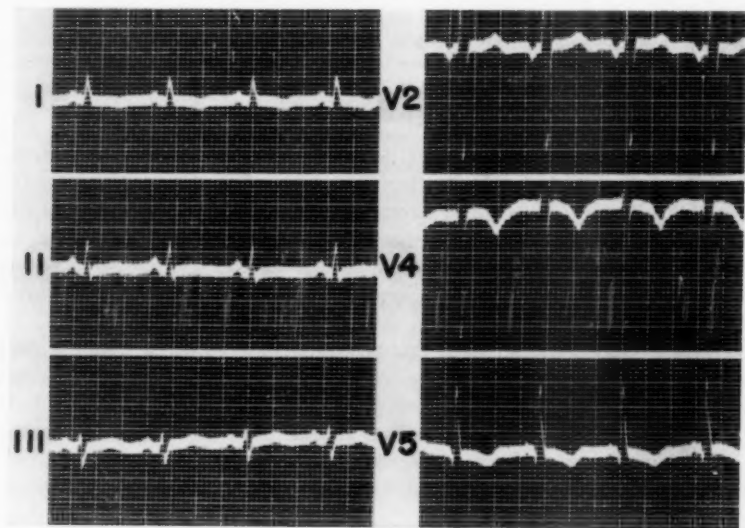


Fig. 11. Case 2. Electrocardiogram. The pattern is largely that of left ventricular hypertrophy.

sedimentation rates were consistently elevated and varied between 18 and 50 mm. per hour. The urine which was originally normal began to show from 3 to 4 plus albumin, many white blood cells and red blood cells. The specific gravity which was normal originally became fixed at 1.012 to 1.016. The total protein diminished to 4.9 grams with 2.37 grams of albumin and 2.53 grams of globulin. The cholesterol was 126 mg. per cent. The serologic tests for syphilis were negative and numerous blood cultures showed no growth. The patient received a long course of penicillin without apparent effect except during periods of pulmonary exacerbation. He was also digitalized and kept on a low sodium diet. At no time did he receive sulfonamides. Among other drugs administered were liver extract, salicylates and sedatives. At one time the patient developed an extensive rash which was traced to bromide. When this drug was stopped the rash cleared. At no time did the patient exhibit any subcutaneous nodules.

He continued to have mild to severe attacks of bronchial asthma and episodes of low back pain with spasm of the lower back muscles. He developed enlargement of the cervical lymph nodes and painful joints. Subsequently the patient developed conges-

tive failure with swelling of the feet and ankles. Before death he complained of severe pain in the bones of the feet. Toward the last of his illness he became disoriented, dyspneic and uncomfortable most of the time. Loss of appetite and weight was striking. His condition deteriorated rapidly and he was found dead in bed on the morning of December 20, 1947.

The autopsy findings were of great interest because of the coincident presence of active polyarteritis nodosa in six or more viscera and classical rheumatic lesions (Aschoff bodies) in the left auricular wall. Lesions resembling Aschoff bodies were also found in or near the vessel walls in the lungs, spleen and the intestine. There were classical lesions of polyarteritis nodosa in the lung, intestine, liver, pancreas, kidney and prostate. There was focal myocardial fibrosis with organizing mural thrombi of the left ventricle and the pulmonary conus. There was rheumatic myocarditis and endocarditis of the posterior left auricular wall. There were small pulmonary emboli and infarcts particularly in the left lower lobe. There was organizing and organized, recurrent fibrinous pneumonia thought to be secondary to the arteriolar and capillary necrosis. There was a hydropericardium of 600 c.c. of straw colored fluid.

Comment: This case provides striking evidence of a diversity of distribution and symptomatology of polyarteritis nodosa. The onset was marked by allergic manifestations including bronchial asthma. The pulmonary picture which was similar or identical to that described in Loeffler's syndrome was associated with unusually high eosinophilia. Later cardiac involvement overshadowed the other manifestations and the patient actually died of congestive heart failure.

In retrospect it would appear that the joint manifestations noted prior to death were doubtless those of active rheumatism. The microscopic examination revealed that in addition to polyarteritis nodosa there was evidence of active rheumatic carditis. This, then, is another instance of the simultaneous or related incidence of rheumatic fever and polyarteritis nodosa in an individual with bronchial asthma, Loeffler's syndrome and a striking eosinophilia.

DISCUSSION

In the cases presented above the incidence of symptoms and findings was similar to other reported series. In addition, however, one of our patients revealed definite radiographic changes in the skull which may or may not have been related to the polyarteritis nodosa. The x-rays of the skull demonstrated areas of diminished density and were reported as suggestive of metastatic malignancy or of the findings encountered in generalized systemic disease. On microscopic examination, also, the findings were equivocal showing destructive changes similar to those of Paget's disease but no evidence of proliferation. There were no vascular alterations in the sections examined. The osseous findings in this patient may, therefore, be present solely as a coincidence.

The comparative incidence of symptoms and findings in the six cases presented above is summarized in the following composite table.

The Incidence of Clinical and Laboratory Manifestations
in Six Cases of Polyarteritis Nodosa

Weakness	100%	Hepatomegaly	50
Persistent fever	100	Anorexia	50
Leukocytosis	100	Headache	50
Anemia	100	Disorientation	50
Weight loss	83	Coma	50
Abdominal pain	83	Lumbar pain	50
Tachycardia	83	Convulsions	33
Muscle pain and tenderness	67	Lymphadenopathy	33
Vomiting	67	Cardiac enlargement	33
Cardiac murmurs	67	Peptic ulcer	33
Dyspnea	67	Abnormal agglutinations	33
Albuminuria	67	Splenomegaly	17
Hematuria	67	Angina pectoris	17
Cylindruria	67	Hemoptysis	17
Hypertension	50	Blindness	17
Joint pains	50	Asthma	17
Nodules	50	Pericardial effusion	17

A few of the findings deserve additional comment. In our six cases there were three instances of subcutaneous nodules and one case each with diffuse brownish pigmentation of the legs, extensive freckling, stellate telangiectasis, purpura, ecchymosis and a greenish tint to the skin.

Joint pain was present in three of the patients and muscle pain and atrophy were severe in one.

One of the patients had thrombosis of the left posteroinferior cerebellar artery and infarction of the left lobe of the cerebellum. Another showed a large hemorrhage into the left median post central cortex which was responsible for his death. During life this patient had repeated epileptiform convulsions. Still another case revealed disorientation and coma for three days prior to death.

There was a high incidence of extensive involvement of the gastrointestinal system. Two of the patients had active peptic ulcers and one of these perforated. The symptoms in two other patients were largely those of abdominal pain, anorexia and weight loss. All of the five cases that came to autopsy showed varying degrees of gross and/or microscopic involvement of the gastrointestinal tract. Three of the patients had hepatomegaly but only one had microscopic evidence of polyarteritis of the hepatic vessels.

Adrenal and testicular lesions were seen in two of our patients and adreno-cortical hyperplasia in one. No changes were seen in the thyroid or pituitary glands.

Microscopic involvement was demonstrated in the lungs of three of the patients while extensive x-ray abnormalities were observed in two. One of these was associated with bronchial asthma and striking eosinophilia of the blood and sputum. The radiologic findings in this case conformed to the criteria laid down for Loeffler's syndrome. Another patient showed prominent fan-shaped infiltrations of the lungs while having cough and bloody sputum.

Cardiac changes were present in all of the five patients who died. One had two episodes of pericarditis with effusion while three had extensive poly-

arteritis nodosa of the coronary vessels with miliary myocardial infarctions. Multiple small aneurysms of the coronary vessels were found in one case. The internal mammary artery showed extensive lesions in one case.

One patient with marked lumbar pain and urinary findings showed at autopsy small renal infarctions and aneurysms of the renal vessels. Similar changes were seen in the testicles and the epididymis of two patients. They were also observed in the arterioles of the cremaster and the vas deferens.

Moderate anemia, leukocytosis and accelerated blood sedimentation occurred in all of the patients. However, eosinophilia of 6 per cent or more was present in only two. In one patient this reached the amazing figure of 82 per cent of 20,000 white blood cells.

Three of the six patients had serum globulin of over 3 grams with reversal of the A:G ratio.

Grossly abnormal electrocardiograms were obtained in three of the six cases. Minor variations were seen in two others. X-ray evidence of striking pulmonary infiltrations was obtained in two of the patients.

It is of some interest that three of the fatal cases received therapeutic doses of sulfonamides during the course of their terminal illness. The causal relationship is, of course, totally unproved. It is likely that three out of any group of five seriously ill patients will have received sulfonamides at some time before death.

In review it may be stated that polyarteritis nodosa is a serious, almost uniformly fatal disease of obscure etiology which appears to be increasing in frequency. As the result of recent and current investigation it seems probable that it is somehow associated with hypersensitivity and related to other diseases of unknown etiology including rheumatic fever, rheumatoid arthritis, nephritis, bronchial asthma and possibly hypertension; that it may be mediated through the adrenal cortex. In view of the fact that this disease or something much like it has been produced in animals following the administration of numerous foreign materials including such therapeutic agents as sulfonamides and sera, it seems reasonable not to employ such potent and potentially noxious drugs in the absence of clear indications.

Because of its widespread vascular distribution numerous organs may be affected resulting in multiple and bizarre symptomatology. However, involvement of the gastrointestinal and genito-urinary systems occurs in practically every instance. Accordingly, complaints related to these systems if accompanied by chronic fever and leukocytosis should suggest the possibility of polyarteritis nodosa. The proved presence of peptic ulcer, however, should not signal the end of a search since it may be merely one finding of a widespread disease. In a similar manner, rheumatic manifestations may co-exist with those of polyarteritis nodosa. Skin findings are common. However, these are varied and except when nodules are present are of little aid in arriving at the correct diagnosis. The so-called classical picture including bronchial asthma and eosinophilia is, in our experience, uncommon.

SUMMARY

1. The historical and etiologic aspects of polyarteritis nodosa are discussed together with a clinical and pathologic description of the disease and a review of the literature.

2. Six cases of this disease are presented together with the autopsy findings in the five who died.

3. The incidence of clinical manifestations and pathologic findings is noted and tabulated.

4. Osseous changes were noted in the calvarium of one of the patients. These changes are described but the relationship to polyarteritis nodosa is not known.

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MASSIVE HEMORRHAGE FROM PEPTIC ULCER: PROGNOSIS AND TREATMENT; CONCLUSIONS DRAWN FROM A LARGE SERIES TREATED IN A MUNICIPAL HOSPITAL *

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THERE is such a decided variation in the degree of symptoms produced by bleeding peptic ulcers that some of those affected do not seek medical assistance, others are attended at their homes, while as a rule only those patients having massive hemorrhage are admitted to a hospital. For the latter the mortality rate is apt to be high, in spite of the fact that their clinical management is under constant supervision. The following report deals with the analysis of autopsy and clinical records of patients with massive hemorrhage from peptic ulcer. In the autopsy series the findings in 41 cases of fatal bleeding are reviewed; and the clinical series includes an analysis of the hospital records of 47 cases of peptic ulcer in which massive hemorrhage was observed. Mortality and the incidence of additional complications are especially emphasized.

In spite of optimism expressed at times concerning advancements made in the treatment of massive hemorrhage from peptic ulcer, the mortality percentages reported by various authors reflect to a large degree the availability of hospital care to the patient. For instance, Goldman¹ gives a mortality rate of 11.1 per cent from exsanguination in a group of 349 patients who entered the San Francisco City and County Hospital because of gross hemorrhage from peptic ulcer. This mortality rate rose to 15 per cent when deaths due to complications of hemorrhage were included. From a group of 182 patients who had been hospitalized because of bleeding from gastric ulcers, Bohrer² selected the records of 80 who had massive hemorrhage, and of these 17.5 per cent died. Hinton³ reviewed the records of 746 patients diagnosed as having gastric or duodenal ulcer. Of these 165 had hemorrhage. The mortality in the latter group was 9 per cent. Bockus⁴ is of the opinion that mortality following massive hemorrhage from peptic ulcer will not exceed 2.7 per cent. Blackford and Cole⁵ however, conclude that in patients who are of the age of 45 years or more, the mortality rate of those who have massive hemorrhage from peptic ulcer will be 30 per cent. Allen⁶ likewise places the mortality from acute massive hemorrhage of older patients at 30 per cent.

Autopsy Series. In the hospital from which this report is made, 13,882 postmortem examinations were carried out during the seven years from

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1938 to 1945. In 41 instances hemorrhage from peptic ulcer was designated as the chief rather than the contributing cause of death. This group consisted of 36 males and five females—the ages varying from 18 to 84 years (table 1). In this group there were two Negroes and three Mexicans.

TABLE I
Ages in Decades of 41 Fatal Hemorrhages
from Peptic Ulcer

10-29	1
30-39	1
40-49	4
50-59	11
60-69	19
70-79	4
80-89	1
	—
	41

Of these patients 38, or 92 per cent, were more than 45 years of age, which is in harmony with the general conclusion that prognosis for such patients is increasingly unfavorable with advancing age. Although seven patients only were specified as being chronic alcoholics, it must be remembered that due to the extreme clinical gravity of the condition of many patients upon admission, several other alcoholics among them undoubtedly were not recognized. As an example of the critical condition of many on entrance, nine patients died during the first day in the hospital, and at the end of their third day a total of 17 out of the 41 patients had died. The remaining patients by this time should have received the benefit of all the supportive measures, including transfusions, yet by the sixth day an additional 11 patients, or a total of 28 out of the 41, were dead. This indicates failure to respond to treatment and shows the relatively long interval that may elapse between the onset of hemorrhage and the advent of death.

Fever was not as frequent as might have been expected. In the 41 patients examined by autopsy and in an additional group of 47 studied clinically, only 10 had a temperature of more than 100° F. during their period of observation. Four of the 10 febrile patients were proved to have bronchopneumonia.

A noteworthy observation is the disproportion between the number of fatalities occurring in patients who had gastric and those who had duodenal ulcers. There were 25 fatal hemorrhages from gastric and 16 from duodenal ulcers. During the fiscal year 1945 to 1946 the diagnosis of peptic ulcer was made in 447 patients. Forty-nine had massive hemorrhage from duodenal ulcer and of these 11 died. Sixteen had massive hemorrhage from gastric ulcer and of these nine died. Bleeding gastric ulcer, although less common than its duodenal counterpart,* carries a higher mortality rate.

* This corresponds with Hurst's experience.⁷ He found that clinically duodenal ulcer occurs three to four times more frequently than gastric ulcer. Stewart,⁸ however, found by a study of autopsy records of 1299 patients who had had peptic ulcer that the incidence was about equal.

Rafsky and Weingarten* found the death rate from bleeding gastric ulcers to be higher than that from duodenal ulcers. In their total of 290 bleeding duodenal ulcers, 20 patients died, while of the 55 with bleeding gastric ulcers 13 failed to survive. Baker¹⁰ concludes that not only is gastric ulcer more difficult to diagnose but it is more likely to cause death from hemorrhage in a ratio of two to one.

The anatomical distribution of bleeding gastric ulcers is the same as that of gastric ulcers in general. In this series, for instance, 14 of the 25 were within 6 cm. of the pyloric ring. This is almost identical to the 59 per cent of 196 gastric ulcers seen at autopsy to be 6 cm. from the pylorus, as reported by Portis and Jaffe.¹¹ The vulnerability of the pylorus to hemorrhage results from frequent ulceration at this site rather than from a predilection for an individual ulcer to bleed.

Aside from the patients who died of exsanguination, there were those in whom complicating disease was an additional finding. In the total of 41 autopsies, four had perforations, three being from gastric and one from duodenal ulcer. Bronchial pneumonia was a terminal complication in six patients. Coronary heart disease with thrombosis or recent infarction was found in five others. Various conditions found, but not intimately related to the bleeding ulcers, are summarized as follows:

Associated Diseases (41 Autopsies)

Far advanced pulmonary tuberculosis	4
Bronchiectasis	2
Acute alcoholism	3
Mitral heart disease	1
Carcinoma of kidney	1
Hypertensive heart disease	1
Pulmonary embolism	1

Hemorrhage, or hemorrhage with shock, was officially designated the sole cause of death in nine of this group of 41 patients. Three of these died within 48 hours after admission to the hospital. The remaining six received the full benefit of medical treatment only to die later at varying intervals. Of these patients 92 per cent were more than 45 years of age.

The incidence of perforation in the group of patients is midway between Bulmer's two perforations in 38 fatal hemorrhages and Goldman's six cases of perforation in 56 deaths due to massive bleeding.

The first of our patients with perforation, a 53-year-old male, was admitted to the hospital with a perforation of one day's duration. A ruptured duodenal ulcer was closed but the patient died from bleeding duodenal ulcer on his fourth hospital day.

The second was a 49-year-old male (Case 1, table 2) who had had melena for one week prior to entry and was diagnosed as having carcinoma of the stomach and possible rupture. His red cell count was 1.4 million and his hemoglobin 18 grams. He received two transfusions of 500 c.c. of blood. At autopsy it was found that an ulcer 6 cm. in diameter, and 4 cm. proximal to the pyloric ring, had perforated.

The third, a 62-year-old male who gave a history of hematemesis two years previously and persistent melena 20 days prior to admission, died of shock on his first

hospital day. Autopsy revealed a perforation of a gastric ulcer 5 cm. proximal to the pyloric ring, and an associated generalized peritonitis.

The fourth, a 66-year-old male, died shortly after admission to the hospital. The clinical impression was that the patient had coronary occlusion and myocardial infarction. A gastric ulcer and a perforating duodenal ulcer with hemorrhage were found at autopsy, but no evidence of heart disease.

Thus in the patient whose condition is critical as a result of hemorrhage from peptic ulcer, the possibility of perforation as a complication cannot be disregarded. Its incidence was 9 per cent in this group.

In those patients who were observed over a period of 8 days in the hospital it is informative to compare the clinical diagnoses with the pathological findings, including significant secondary complications. This group consisted of 11 patients, in one of whom (Case 6) the hemorrhage occurred while in the hospital (table 2).

Patients 1 and 10 exemplify a mistaken clinical diagnosis of carcinoma of the stomach as the cause of hemorrhage. Naturally such errors in the choice of diagnosis in middle-aged and elderly patients are understandable, but statistically the odds are in favor of peptic ulcer. Of Bulmer's 133 patients who had hematemesis¹² 117 had ulcer and only three had cancer. In Schiff's report of hematemesis and melena¹³ the incidence of peptic ulcer was 51.1 per cent, as compared to 3.1 per cent for carcinoma. In a study of the underlying causes of hematemesis from this hospital Thompson¹⁴ found that bleeding from peptic ulcer was responsible for 48.1 per cent, as compared to 3.4 per cent from carcinoma. So when the diagnosis is obscure, the choice of ulcer should take precedence over cancer, and the patient usually benefits from this decision because a more prompt, determined supportive therapy is initiated.

When the differential diagnosis lies between bleeding esophageal varices and bleeding peptic ulcer (Cases 4 and 7), the disparity found in this institution is not too great, since 32.2 per cent of cases of hematemesis were from the former cause.

Clinical Series. In order to obtain a different perspective, the clinical records of a large group of peptic ulcer cases were studied. During the years 1945 and 1946, 54,593 patients were admitted to the Los Angeles County Hospital. Of these 636 had either proved or probable peptic ulcer. A diagnosis of ulcer was established by x-ray or surgery in 447. In this latter number there were 65 instances of massive bleeding. In 49 instances there was massive bleeding from duodenal ulcer and in 16 from gastric ulcer. Of those who had hemorrhage from duodenal ulcer, 11 succumbed, a mortality of 20 per cent, while nine of those who bled from gastric ulcer died, or 56 per cent. The mortality from the entire group who had hemorrhage from gastric and duodenal ulcer was 30 per cent, which, when compared with other published statistics regarding incidence of death, is unusually high. However, this again reflects the degree of severity of the patients' symptoms before admission to the hospital.

TABLE II
Clinical Diagnosis and Pathological Findings

Case	Age Sex	Hosp. Days	
1	49 M	11	C.D. Carcinoma of stomach with metastasis, possible rupture. PM. Gastric ulcer lesser curvature 4 cm. proximal to pyloric ring, 6 cm. diameter, 2 mm. depth. C Perforation; acute generalized peritonitis.
2	66 M	8	C.D. Bronchial pneumonia, atypical ulcer with hemorrhage, severe anemia. PM. Duodenal ulcer 1 cm. from pyloric ring, 4 by 4 cm. C Bronchial pneumonia.
3	84 M	15	C.D. Arteriosclerotic heart disease, malnutrition, possible gastric carcinoma with obstruction. PM. Duodenal ulcer 2 cm. diameter, 9 mm. depth. C Acute confluent bronchopneumonia.
4	58 M	9	C.D. Hemorrhage esophageal varices, cirrhosis of liver. PM. Gastric ulcers—3 ulcers lesser curvature. C Cerebral edema (alcoholism), liver normal.
5	18 M	9	C.D. Gastrointestinal hemorrhage of unknown origin, cerebral anox- emia. PM. Duodenal ulcers, 3 ulcers near pyloric valve. C None (2 previous admissions for hemorrhage in 4 years).
6	60 M	4 mo.	C.D. Respiratory failure due to coronary occlusion, amebic dysentery, hypertension. PM. Gastric ulcer of cardia 4 cm. diameter. C Coronary sclerosis without infarction.
7	50 M	16	C.D. Hemorrhages from possible esophageal varices—6/25/41. PM. Gastric ulcer, erosion of gastric artery, mid-stomach—6/30/41. C Jejunostomy, pyloroplasty—6/18/41—patient continued to bleed. Total transfusion 3500 c.c.
8	60 M	14	C.D. Cerebral thrombosis or coronary thrombosis due to bleeding peptic ulcer. PM. Gastric ulcer 1 cm. from pylorus. C Bronchial pneumonia.
9	54 M	9	C.D. Chronic fibroid tuberculosis, chronic gastric ulcer with obstruc- tion. PM. Duodenal ulcer 10 by 5 cm., adjacent to pyloric ring. C Pulmonary tuberculosis, bilateral, far advanced.
10	59 M	14	C.D. Coronary heart disease, generalized arteriosclerosis, bleeding duodenal ulcer. PM. Gastric ulcer 1 cm. in diameter. C Diffuse scarring of myocardium without evidence of infarction. Heart weight 500 gm.
11	69 F	9	C.D. Anemia, secondary to carcinoma of stomach, toxemia due to carcinoma. PM. Gastric ulcer 4 cm. proximal to pyloric ring, 3 by 3 by 1 cm. C Rheumatic mitral disease (ulcer pains for past 5 yrs.)

C.D.—Clinical diagnosis.

PM.—Postmortem findings.

C —Complications.

The charts of 47 of these 65 patients with severe bleeding were made available for study. Of these, 37 had duodenal and 10 had gastric ulcers. The sex incidence was as follows: duodenal ulcer, 28 males and 9 females; gastric ulcer, 7 males and 3 females. Variation in age was from 28 to 79 years. The three youngest fatalities in this clinical group were patients who were between 50 and 60 years of age. This affirms the mounting risk from massive hemorrhage from the fifth decade on.

Not infrequently in patients past 60 years of age with bleeding peptic ulcer there is no history of preceding characteristic ulcer symptoms. Three instances of this kind were observed in the 18 patients of this clinical group who were 60 years or older.

The first, a 64-year-old white male who gave a history of indigestion during the six months prior to his hemorrhage, was noted to have a gastric retention when studied with x-ray. The clinical diagnosis was probable gastric carcinoma, cachexia and anemia, but postmortem examination revealed a prepyloric ulcer 4 cm. in diameter, with a bleeding vessel at its base. The second, a 76-year-old male, gave no history whatsoever of ulcer, and survived for 36 hours in the hospital. The clinical diagnosis was shock and probable bleeding peptic ulcer. At autopsy two duodenal ulcers were found, one anterior and one posterior. In the base of the anterior ulcer an eroded, open artery was present. The third patient was a 65-year-old male who was admitted because of acute urinary retention, and hemorrhage occurred in the hospital. The clinical diagnosis was probable neoplasm of the gastrointestinal tract and benign prostatic hypertrophy. Postmortem examination revealed a duodenal ulcer with massive hemorrhage and marked prostatic hypertrophy.

Surgery was performed on five of the 47 patients in each case a partial gastrectomy being done, and there were no postoperative fatalities.

Meyer, Sorter and Necheles¹⁵ recommend that surgery for the correction of hemorrhage from peptic ulcer be restricted to those over 45 years of age because of the unusually high percentage of recovery among younger patients. Mathewson and Pinkham¹⁶ recommend surgery for acute massive hemorrhage for those past 50, but in their experience of 18 emergency operations on patients of this age their surgical mortality was 15.7 per cent. This is not a significantly lower mortality than that achieved with medical management. Moreover deaths from hemorrhage in patients under 50 are not uncommon.

Excluding the complications of perforation (the incidence of which was 9 per cent in those who were examined post mortem and which necessitates the consideration of surgical exploration), the great majority of deaths were naturally due to exsanguination and circulatory failure. In order to improve the welfare of this type of patient, special attention must be given to the control of massive hemorrhages occurring in those past 50 years of age. By comparison their condition is more critical than that of patients of similar age suffering from coronary thrombosis or pneumonia; although such conditions are often concurrently present, as five of the 41 patients were noted to have coronary heart disease. It is important also to bear in mind that our

knowledge of the features of shock in other emergencies is not entirely applicable to this one, for hemorrhage can be insidious, depending upon its duration and intermittency.

There are occasions when a sudden hemorrhage is not accompanied by a rapid pulse or lowering of the blood pressure. Shenkin and his co-workers¹⁷ withdrew over a liter of blood from volunteers without causing signs or symptoms as long as the subjects remained recumbent. Wallace and Sharpey-Schafer¹⁸ bled 27 convalescent patients as much as 1150 c.c. and of this group the blood pressures of 16 fell, and in one-half of these was depressed less than one hour. The cardiac rates of the entire group were recorded as slowed, increased, or unchanged. The time required for the hemoglobin determinations to reach their maximum dilution varied from three to 90 hours, with an average time of 32 hours. Accurate observations such as these are informative but not necessarily applicable for patients who have slowly bled for hours, or even days, nor do these experiments make allowances for a previously-existing narrowed and sclerosed coronary arterial system (Kinney and Mallory¹⁹). These cardiac patients are unable to respond to the increased physiological demand, and congestive heart failure or coronary insufficiency will supervene. Stead²⁰ has made observations on the cardiac output in congestive failure and found it to be low, but in the two patients having severe anemia with congestive failure, the cardiac output was increased. Nobel and Gregersen²¹ determined the blood volume in patients with hemorrhage soon after injury, with clinical evidence of shock, and found it to be reduced from 30 to 90 per cent below normal. As a rule, 1.5 to 2 liters of blood were required for replacement. Even when corrected, however, the blood volume is restored by the medium of the flow of plasma proteins into the blood stream from storage reserves (Beattie and Collard²²). When the patient has exhausted his protein reserve either by starvation or chronic bleeding, the replenishment of his blood volume is then entirely dependent upon additional sources, either supplied from amino acids by mouth or by the parenteral route. Hematocrit and hemoglobin determinations in this emergency are not trustworthy indices for the estimation of the circulatory blood volume or the existing degree of oligochromemia (Ling and Sprinz²³). Whole blood is preferable to plasma because it not only adds more proteins but also increases the oxygen capacity.

A neglected observation upon this group of patients is their urinary output. The normal resting subject diverts approximately 20 per cent of his total circulating blood through the kidneys. In shock there is a proportionally greater reduction of renal blood flow than of cardiac output. Lassen and Husfeldt,²⁴ observing normal subjects under spinal anesthesia, noted that urinary output is drastically curtailed with hypotension and that anuria takes place when the systolic blood pressure approaches 60 mm. of mercury. Further, Lawson et al.,²⁵ investigating the renal circulation in patients with shock, found the glomerular filtration and effective renal plasma flow to be significantly reduced in nearly every case. Oliguria was observed in nearly

all patients in shock. In some of the more severe cases, complete anuria occurred and it was not until the general circulation had improved as a result of treatment that the urine flow was resumed. More pertinent are the conclusions of Corcoran and Page²⁶ who noted that transfusion would restore renal blood flow and function, but restitution of renal blood flow, as well as arterial pressure, was progressively less adequate with succeeding periods of hypotension.

How may the prognosis of this type of patient be improved? In this group, fluids and blood transfusions were promptly administered, and the Sippy or modified Meulengracht diets ordered at varying intervals. Too much reliance, however, was placed upon the blood counts, packed-cell volumes, and plasma protein levels as a guide of the patient's condition without cognizance that these tests make no allowances for hydration or malnutrition. The duration of acute symptoms and the appearance of the patients are just as important as the laboratory evaluations. The appearance of the tongue, turgor of the skin, eyeball tension, are significant signs of dehydration. Another guide to the patient's condition is the urinary findings. When oliguria accompanied by a low specific gravity is noted, it is an unfavorable sign. In the majority of such instances, this is best corrected by additional transfusion, which not only restores the blood volume but also compensates for a defective coronary circulation, so prevalent in the older patient. Transfusions of 1500 c.c. of blood are more apt to meet the physiological demand than smaller quantities. The danger of a transfusion reaction of matched blood is far less than the incidence of clinically unrecognized coronary insufficiency in this series. The failure fully to restore these patients from shock is regarded as the important clinical omission.

SUMMARY

1. In 41 consecutive necropsies of patients whose death was attributed primarily to bleeding from peptic ulcer, 38, or 92 per cent, were over 45 years of age. A clinical survey of 47 patients having bleeding peptic ulcer disclosed no fatalities in those under 50 years of age.
2. Massive hemorrhage from gastric ulcer as a rule is more hazardous than bleeding duodenal ulcer, the attending mortality being found in a ratio of two to one.
3. The usual complications accompanying bleeding peptic ulcer were bronchopneumonia, coronary thrombosis with or without recent infarction, and perforation. Cerebral anoxemia was not differentiated as a complication but was included as a symptom of exsanguination.
4. A diagnosis of congestive failure or coronary insufficiency without recognition of the rôle of anemia as the precipitating cause, and somewhat less frequently a diagnosis of malignancy, increases the mortality rate of these patients because of misguided therapy.

5. There are no readily available tests, nor completely satisfactory signs, to confirm a persistent shock and as a result, therapeutic measures may not be instituted to compensate fully for the physiological demands of the older patient.

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TORULOSIS OF THE CENTRAL NERVOUS SYSTEM: REVIEW OF LITERATURE AND REPORT OF FIVE CASES *

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TORULOSIS of the central nervous system has been known for more than half a century and has been reported from almost every country in the world. As early as 1861, Zenker¹⁰⁷ reported the case of a man who died as the result of a fungus infection of the central nervous system. It is possible that the causative organism in this case was *Torula histolytica*. Von Hansemann¹⁰¹ in 1905 reported a case of meningitis in which small gelatinous cysts containing yeast cells were present in the meninges. In 1916, Stoddard and Cutler's monograph⁹¹ established the clinical and pathological picture of torulosis. By 1925, Shapiro and Neal⁸⁵ were able to collect 15 cases from the literature. In 1931, Freeman³² reviewed the 43 cases which had been recorded in the literature up to that time. Subsequent reviews have been made by Levin⁸⁴ in 1937, Binford¹⁰ in 1941, and by Voyles and Beck¹⁰² in 1946.

The purpose of this paper is to report five cases of central nervous system torulosis, to review the literature of central nervous system torulosis and to analyze the cases reported since the paper of Voyles and Beck in 1946.

CASE REPORTS

Case 1. A white male, age 51, was admitted to the medical service at the University Hospital on September 16, 1938. He complained of pain in the legs, arms, and neck, felt dizzy, and was unstable on his feet with a tendency to fall to the left. He had been admitted to the Union Memorial Hospital in July, 1937 where a diagnosis of benign lymphocytic choriomeningitis had been made. Spinal fluid at that time showed 157 white blood cells with 87 per cent lymphocytes. Routine cultures were reported negative. Spinal fluid studies done by the Public Health Service showed a strong protection against the virus of choriomeningitis. He continued to have difficulty in walking and in February, 1938, he began to lose weight, developed pains in the legs and had reversal of the sleep pattern. He developed dizzy spells. In September, 1938, his eyes were noted to have a glassy appearance and when he attempted to walk he fell to the left. His speech became thick and he developed a tremor of both hands.

Examination on admission to University Hospital showed evidence of weight loss. He was disoriented, restless, and slightly opisthotonic. The lens of the right eye was cloudy. Examination of the fundi showed slight congestion of the retinal veins with no evidence of choking. He had nuchal rigidity with a positive Kernig. The deep tendon reflexes were normal in the upper extremities, knee jerks hypoactive, abdominal and cremasteric reflexes absent, and the plantar responses were equivocal.

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Laboratory Findings: Roentgen-ray of the chest was negative. The urine showed a trace of albumin. Blood: Hemoglobin 85 per cent, red blood cells 4,600,000, white blood cells 8,650; 80 per cent polynuclears, 18 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophiles. Blood sugar was 98 mg. per cent, non-protein nitrogen 30 mg. per cent. Serological tests for syphilis were negative. Spinal fluid showed pressure 168 mm. water, 52 polynuclears, 48 lymphocytes, globulin three plus, quantitative protein 84 mg. per cent, sugar 14 mg. per cent. The spinal fluid was xanthochromic.

Course in Hospital: Various diagnoses were made. Exploratory trephines were done at which time the leptomeninges were found to be opalescent. Sulfanilamide was given for two days. The patient became more stuporous, developed congestive changes in the lungs. The temperature rose to 101.6° with a respiratory rate of 40. He died on October 1, 1938.

Comment: This patient's illness was of eight months' duration. The clinical course was characterized by headache, root pains, ataxia, signs of meningeal irritation, mental confusion, and stupor. The diagnosis of benign lymphocytic choriomeningitis was made 15 months prior to death based on the finding by the Public Health Service of a strong protection against the virus of choriomeningitis. Spinal fluid cultures were reported as negative in July, 1937. After admission to the University Hospital the spinal fluid cultures showed no growth but the fluid was cultured for only two days. Because of the diagnosis of benign choriolymphocytic meningitis having been made by the Public Health Service laboratory, brain tissue was sent to this laboratory and the correct diagnosis of torulosis of the central nervous system was made. Further study of autopsy material showed *Torula* in the adrenal glands and meningo-encephalo-ependymitis of the brain. The clinical diagnosis was missed because the disease was not suspected.

Case 2. A white male, age 34, was referred to the University Hospital on June 28, 1945 by Dr. Harry B. Thomas, York, Pennsylvania. Present illness began seven weeks prior to admission with lassitude and coryza followed by dull occipital headache. Visual acuity progressively diminished so that two weeks after the onset of the illness he had to cease working as a truck driver. He was admitted to the York Hospital on June 22, 1945. On June 27, 1945 bilateral choked discs were noted and the patient was transferred to University Hospital.

Examination showed moderate nuchal rigidity and a low-grade nasopharyngitis. Blood pressure 150/80 mm. Hg, temperature 97.8°, pulse 54, respirations 20. The patient was confused and lethargic with slurred speech. There was approximately 40 per cent loss of motor power in all muscle groups of the left upper and lower extremities. On ophthalmoscopic examination, one-half diopter choking was noted on the left and one diopter on the right.

Laboratory Findings: Roentgen-rays of the skull and chest were negative. Blood showed hemoglobin 114 per cent, white blood cells 8700, with a differential of 68 per cent polynuclears, 22 per cent lymphocytes, 10 per cent monocytes. The blood sugar was 84 mg. per cent, and the urea nitrogen 26 mg. per cent. Serological tests for syphilis were negative.

Course in Hospital: On June 29, 1945, bilateral occipital trephines and ventriculography was performed. The ventricular system was found to be within normal limits. The ventricular fluid was xanthochromic and laboratory analysis of this fluid showed globulin one plus, 200 cells resembling lymphocytes, 80 cells showing budding.

Torulosis was suspected and the spinal fluid was cultured on Sabouraud's medium. Within 12 hours a heavy growth of *Cryptococcus neoformans* was present.

Following ventriculography the patient remained irrational and confused. On July 4, 1945, he was placed on Furacin, two grams orally every 15 hours. A specimen of spinal fluid withdrawn on July 9, 1945 was examined qualitatively for Furacin and found to be positive. On that day a Furacin sensitivity test was begun and it was found that the drug was not efficacious against the *Cryptococcus neoformans* in vitro.

During the early morning of July 11, 1945, the patient lapsed into coma, with slow pulse and labored respirations. At 8:00 p.m. on July 11, 1945, he died.

Comment: The duration of this patient's symptoms was nine weeks from inception to death. Headache, diminished visual acuity, papilledema, mental disorientation and confusion strongly suggested a frontal lobe tumor. After normal ventriculographic findings, examination of the ventricular fluid led to the presumptive diagnosis of Torula meningitis. This was substantiated by culture. Autopsy showed diffuse meningo-encephalitis with plexitis and ependymitis. An unusual finding was ischemic necrosis of the adenohypophysis. No evidence of torulosis was found outside the nervous system. Furacin (5-nitro, 2-furaldehyde semicarbazone) came to our attention because of its fungicidal properties. The patient was treated with this drug alone without effect.

Case 3. A white female, age 36, was admitted to the service of Dr. T. Nelson Carey at University Hospital on August 20, 1945. In 1942, she had complained of headaches severe enough to warrant hospitalization for a two week period. Nine weeks after onset, the headaches disappeared and she then remained symptom-free until July, 1945. During the six weeks preceding admission she had early morning nausea and vomiting associated with constipation and urinary hesitancy.

On examination the only positive findings were unsustained left lateral nystagmus, slight protrusion of the tongue to the left, and a slightly positive Romberg test. Temperature was 99, pulse 70, respirations 20, and blood pressure 120/80 mm. Hg.

Laboratory Findings: Roentgen-ray of the skull was negative. A chest film showed thoracic scoliosis. Urine showed occasional white blood cells. Blood: Hemoglobin 91 per cent, white blood cells 7300; 70 per cent polynuclears, 22 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophiles. Blood sugar 54 mg. per cent, urea nitrogen 10 mg. per cent. The blood serologic tests for syphilis were negative.

Course in Hospital: On August 30, 1945 lumbar puncture was performed. Initial pressure was 280 mm. of water. The spinal fluid was clear and colorless and contained 80 white blood cells of which 90 per cent were lymphocytes and 10 per cent were polynuclears. Globulin was three plus, quantitative protein 127 mg. per cent; and the serologic tests for syphilis were negative. Subsequent lumbar puncture revealed sugar 18 mg. per cent. Torulosis was suspected. Spinal fluid obtained at lumbar puncture on September 13, 1945 yielded positive culture on Sabouraud's medium of *Cryptococcus neoformans*. Sensitivity tests were made on the organism isolated from the spinal fluid and it was found to be resistant to penicillin and to streptomycin.

Many therapeutic measures were employed: calcium gluconate, potassium iodide, sodium iodide, sulfadiazine, intramuscular and intrathecal penicillin, intramuscular and intrathecal streptomycin, thiamin, and diazone. Typhoid fever therapy was instituted and she received 71 hours over 100°, 40.5 hours over 102°, and 10 hours over 104°. On October 27, 1945 during a lumbar puncture after approximately 5 c.c. of spinal fluid had been removed, the patient stated that she felt as though she was going to faint, and then developed mild opisthotonos and lapsed into coma. Following carbon

dioxide inhalations and intramuscular coramine she regained consciousness within six hours. Trephines and ventricular puncture were contemplated had she not regained consciousness.

Between mid-December, 1945 and mid-January 1946 she suffered from excruciating headache which required codeine, pantopon, and demerol for relief of pain. Also during this period she was unable to take adequate diet by mouth and had to be maintained parenterally. Due to its fungicidal properties the use of sodium caprylate was contemplated, but toxicity experiments on intrathecal administration in dogs contraindicated its employment. The idea of alkalization therapy was conceived and on March 19, 1946 the patient was placed on a restricted chloride diet, sodium bicarbonate gr. 80 per day orally, sodium bicarbonate gm. 7.5 per day intravenously, and citrocarbonate drachms 12 per day orally. The dose was gradually increased until she was receiving sodium bicarbonate gr. 400 per day orally, sodium bicarbonate gm. 28 per day intravenously, and citrocarbonate drachms 16 per day orally.

The patient improved. Spinal fluid pressure which previously had been as high as 380 mm. water fell to 150 mm. water. White blood cells which previously had been as high as 1,200 fell to 2, 3, and 4 lymphocytes on lumbar punctures in May, 1946; and on June 5, 1946 the spinal fluid white blood cell count was 0. The spinal fluid sugar returned to normal but the protein remained elevated. No positive spinal fluid cultures were obtained following institution of alkalization therapy, but there had been one negative spinal fluid culture two months prior to alkalization. The patient was able to be up and about on May 3, 1946. Under alkalization therapy her carbon dioxide combining power rose to as high as 63 vol. per cent and averaged 59 vol. per cent. The spinal fluid pH rose from an initial reading of 7.0 to as high as 7.85. She appeared to suffer no ill effects and improved clinically as well as from a laboratory point of view. She was discharged on August 5, 1946 and instructed to take sodium bicarbonate gr. 200 orally per day.

She was readmitted to the University Hospital on December 20, 1946 for follow-up lumbar puncture. She appeared clinically well at that time and complained only of ringing in her ears. Despite repeated attempts it was impossible to enter the lumbar subarachnoid space.

In March, 1947, 18 months after initial admission to the University Hospital, she developed weakness, pain, numbness, tingling, and hypersensitivity of her lower extremities. Tinnitus was no longer present. When the pain became severe enough to warrant administration of demerol, she was again admitted to the University Hospital on August 18, 1947. On examination at that time there was slight unsustained lateral nystagmus to the right, a suggestion of saddle anesthesia, and spotty areas of hypesthesia and hyperesthesia of the lower extremities. The knee jerk and ankle jerk were greater on the left than on the right. An impression of arachnoiditis of the cauda equina was made. She was given roentgen-ray therapy to the lumbar region, and again discharged.

Several weeks later she began having seizures in which she would have a sudden onset of headache and dizziness, sometimes associated with vomiting. This was followed by several minutes of unconsciousness. Between these seizures she was asymptomatic except for the disturbance in gait which persisted. She was treated with dilantin sodium but the attacks of syncope continued to occur. On September 1, 1948 she had such a seizure and died in her home.

Comment: This patient's illness was of 38 months' duration. Three years prior to the presumed date of inception she was admitted to a hospital for investigation of severe headaches. Lumbar puncture was not performed at that time.

Her presenting complaints of nausea and vomiting in the presence of nystagmus and faintly positive Romberg test suggested a cerebellar tumor. Torulosis was suspected when it was found that she had a cerebro-spinal fluid pleocytosis and the diagnosis was confirmed by culture of the cerebro-spinal fluid. Many therapeutic agents were employed and it is difficult to assay the relative value of each of these. She did, however, appear to improve clinically after the initiation of alkalinization therapy. Her clinical remission five months after admission was accompanied by a return of her cerebrospinal fluid to approximate normality, with negative cultures. Following her discharge from the hospital 12 months after admission it was not possible to obtain spinal fluid again by lumbar puncture. Eighteen months after admission, weakness, pain, numbness, tingling and hypersensitivity of her lower extremities developed. One wonders whether the cauda equina symptoms were due to torulosis or secondary to intrathecal penicillin and streptomycin which she had received. The cauda equina lesion was treated with roentgen irradiation and some improvement followed, although an unsteady gait persisted until death. During the last year of her life, she had seizures characterized by sudden onset of headache, dizziness, and occasionally vomiting, followed by several minutes of unconsciousness. She died during one of these attacks of syncope. At autopsy no evidence of torulosis was found. The meninges in the lumbar region were markedly thickened, a moderate internal hydrocephalus was present, and "violin string" adhesions were noted in the fourth ventricle. Examination of ventricular fluid obtained under aseptic conditions at time of autopsy showed no evidence of torulosis. The ventricular fluid contained 18 lymphocytes, quantitative protein 42 mg. per cent, sugar 21 mg. per cent, and all smears and cultures were negative.

Case 4. A white male, age 37, referred to the University Hospital on June 13, 1946 by Dr. D. D. Caples, Reisterstown, Maryland. He complained of headache, nausea, vomiting, loss of appetite, weakness, and unsteadiness on his feet of one week's duration. He had been in bed for three days preceding admission and had taken nothing but fruit juices. The patient had been rejected by the army because of a healed tuberculous focus in one lung. He remembered no such infection. On examination the only positive finding was unsteadiness of gait which was thought to be due to generalized weakness, slight cervical rigidity, and suggestive Kernig and Brudzinski signs.

Laboratory Findings: X-ray of sinuses showed mild sinusitis, right antrum. X-ray of chest showed a small partially calcified area of infiltration in the right base. Urine showed a trace of sugar. Blood showed hemoglobin 103 per cent, white blood cells 9,950, with a differential of 77 per cent polynuclears, 20 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophiles, blood sugar 87 mg. per cent, urea nitrogen 18 mg. per cent. Serological tests were negative.

Course in Hospital: On the day following admission a lumbar puncture was done showing an initial pressure of 290 mm. water. The spinal fluid was clear and colorless and showed 396 white cells of which 92 per cent were lymphocytes, 4 per cent were polynuclears, and 4 per cent were abnormal lymphocytes. Globulin was one plus, quantitative protein 129 mg. per cent, and sugar 53 mg. per cent. A guinea pig was

inoculated with a specimen of sputum from the patient. No lesions were found when the animal was autopsied. The temperature, which had varied between 98.0 and 100.0 since admission rose to 102.2° on the sixth hospital day, and the patient was placed on penicillin. The cells in the spinal fluid which the laboratory had called abnormal lymphocytes were thought to be *Cryptococcus neoformans*, and alkalization therapy was begun on June 21, 1946. On July 9, 1946, the spinal fluid cultures taken on June 14 and June 18 were noted to show colonies of *Cryptococcus neoformans*.

Blood carbon dioxide combining power determinations were made frequently while alkalization therapy was being administered. Carbon dioxide combining power varied between 49 and 70 volumes per cent. He seemed to suffer no ill effects from this high level and appeared clinically better when it was in the middle 60's. Penicillin was administered throughout the remainder of his hospital stay.

Repeated lumbar punctures were done and cultures were taken every week. By the middle of September, three months after admission, the spinal fluid pressure had returned to normal limits. Culture of the spinal fluid for Torula organisms was positive intermittently until September. Culture of spinal fluid specimens collected on September 6, September 14, and September 19 were negative for *Cryptococcus neoformans*.

The patient was ambulatory during the latter part of August and throughout September until he was discharged. His only complaint during the last month of his hospitalization was morning headache, which gradually disappeared. On September 23, 1946, he was discharged from the hospital.

The patient was re-admitted to the same hospital on December 19, 1946 complaining of nausea and severe headaches of two weeks' duration. The headaches were not relieved by medication. During the week preceding admission his vision had become blurred. Ophthalmoscopic examination revealed two diopters choking bilaterally. There was mild cervical rigidity. Examination was otherwise negative. Lumbar puncture was performed on the evening of admission and revealed a spinal fluid pressure of 355 mm. water. Laboratory analysis of fluid showed 72 lymphocytes, globulin four plus, quantitative protein 180 mg. per cent, and sugar 5 mg. per cent. Spinal fluid cultures were positive for *Cryptococcus neoformans*. The patient gradually became confused and developed spontaneous twitches of the arms and legs. On December 20, alkalization was begun. On December 27 lumbar puncture was repeated and an initial pressure of 300 mm. water noted. The fluid was xanthochromic. Lumbar punctures were repeated periodically. Mental confusion characterized the patient's condition. It became more and more severe. The patient went progressively downward. On December 31, 1946 the patient suddenly became cyanotic after several hours of Cheyne-Stokes respirations, and he died shortly thereafter.

Comment: The duration of this patient's symptoms was seven months from inception to death. Headache, nausea, vomiting, anorexia, generalized weakness, unsteadiness of gait, and cervical rigidity developing within one week of admission suggested meningitis, and when his temperature rose to 102.2° penicillin was administered. Examination of the cerebrospinal fluid led to the presumptive diagnosis of Torula meningitis. This was substantiated by culture. He was placed on alkalization therapy. Three months following admission, he was asymptomatic and his cerebrospinal fluid showed no evidence of torulosis. He was discharged from the hospital and returned to work only to return to the hospital three months later with headache, vomiting, cervical rigidity, choked discs. Spinal fluid cultures were again positive for *Cryptococcus neoformans*. There was no response to al-

kalination therapy at that time. Autopsy showed a primary ependymitis with plexitis, blockage of the aqueduct cerebri and marked internal hydrocephalus, the brain weighing 2100 grams. No evidence of torulosis was found outside the central nervous system.

In this case again a remission occurred but whether this was spontaneous in origin or due to alkalinization or penicillin cannot be stated.

Case 5. A white male, age 18, was referred to University Hospital on May 27, 1948 by Dr. S. Robert Wells, of the Washington County Hospital, Hagerstown, Maryland. In 1945, he developed large painful cervical adenopathy which regressed following x-ray therapy. The cervical adenopathy recurred in March, 1947 and disappeared promptly following another course of x-ray. A biopsy of one of the cervical glands at that time showed chronic lymphadenitis. He was then without complaints until April, 1948 at which time he began to have transient episodes of rheumatic pain in the joints of his lower extremities with inability to walk and swelling of the lower legs. At approximately this time the patient also noticed for the first time glands in the axillae and groins which were painful. Shortly thereafter he developed severe generalized headache, occasionally accompanied by nausea and vomiting. He was admitted to the Washington County Hospital on May 12, 1948, where two lumbar punctures were done. These disclosed normal pressure, xanthochromic fluid, increase in white cells predominantly lymphocytes, globulin three plus, protein elevated, sugar lowered. Cultures were reported as negative. X-rays of the skull and femora were negative. X-rays of the chest suggested a resolving atypical pneumonia. Temperature rose to 99°, white blood cell count was 14,500 and sedimentation rate was 18 mm. On the basis of these findings coupled with slight nuchal rigidity, the patient received penicillin, sulfadiazine, and streptomycin. A sample of the cerebrospinal fluid was forwarded to the Baltimore City Health Department and the patient was transferred to University Hospital on May 27, 1948.

On examination at time of admission he was found to be poorly nourished and drowsy but cooperative. Temperature was 100°, pulse 80, respirations 20, blood pressure 114/80 mm. Hg. Ophthalmoscopic examination showed no papilledema but the vessels were tortuous and somewhat full. Horizontal nystagmus was present, more on the right than on the left. There was also minimal right central facial weakness. A moderate degree of nuchal rigidity was present and the Kernig's sign was positive.

Laboratory Findings: X-ray of the chest showed small areas of infiltration behind the left second and third interspaces. A large area of infiltration was on the left just above the diaphragm. Urinalysis was negative. Blood showed hemoglobin 99 per cent, white blood cells 13,250, with a differential of 77 per cent polynuclears, 15 per cent lymphocytes, 9 per cent monocytes, urea nitrogen 14 mg. per cent, blood sugar 90 mg. per cent. The blood serologic tests for syphilis of both the patient and his mother were negative. Lumbar puncture was performed on May 28, 1948. The spinal fluid showed a pressure of 175 mm. It was somewhat cloudy and contained 706 white cells of which 68 per cent were lymphocytes and 32 per cent were polynuclears. Globulin three plus, quantitative protein 120 mg. per cent, sugar 17.5 mg. per cent, serologic test for syphilis positive. Two days later eight colonies of *Cryptococcus neoformans* were noted on Sabouraud's media. A letter was received from the Washington County Hospital stating that the bacteriological report on the spinal fluid of May 21, 1948, forwarded by them to the Baltimore City Health Department, was positive for *Cryptococcus neoformans*. On June 1, 1948 a mouse was injected intracerebrally with a suspension obtained from a broth culture of this organism. The mouse died on June 11, 1948, and pathological examination of its brain showed typical *Torula* lesions.

Course in Hospital: The patient received streptomycin from June 3, 1948 to June 13, 1948. He failed to improve and cultures became more strongly positive. On June

14, 1948 alkalinization therapy was begun. On June 17, 1948 it was noted that he was more lethargic and disoriented. The ptosis on the left was marked and there was weakness of internal gaze on the left. His general condition failed to improve and it was decided that fever therapy should be used. A fever cabinet was employed with the intent of maintaining his temperature at 104° for 120 hours. After preliminary blood studies were made, he was given thiamine chloride, ascorbic acid, choline dihydrogen citrate, kayquinone, and a blood transfusion. On June 28, 1948 the patient was placed in the fever cabinet and an attempt at fever therapy was begun. Due to faulty mechanics of the apparatus employed, his temperature rose to 107.8° within 50 minutes. His temperature was lowered by mechanical means and it was elected that further attempts at fever therapy should be deferred.

The patient's general condition did not improve. On July 4, 1948 he was disoriented and lethargic with generalized weakness. On July 6, 1948 his temperature rose to 101°, pulse 100, respirations 30. At 6:00 p.m. on July 6, 1948 his respirations ceased.

Comment: This patient's illness was of three months' duration although cervical adenopathy had been present three years preceding onset of cerebral symptoms. The clinical course was characterized by headache, nausea, vomiting, stupor, and cervical rigidity. The diagnosis was suspected in the presence of an unexplained spinal fluid pleocytosis, and was confirmed by culture of the cerebrospinal fluid. The course of the disease was not altered by streptomycin or alkalinization therapy. An unsuccessful attempt was made to combine alkalinization with prolonged hyperthermia. Autopsy showed diffuse Torula meningo-encephalitis associated with generalized moniliasis. *Monilia albicans* was cultured from granulomatous pulmonary lesions. Cerebral moniliasis co-existed with the torulosis.

DIAGNOSIS

Torula meningitis is a chronic inflammatory disease owing to invasion of the central nervous system by the fungus, *Cryptococcus neoformans*. This disease presents a protean neurological picture. The diagnosis of Torula meningitis cannot be made on a basis of signs and symptoms. The symptoms may suggest a pyogenic, luetic, tuberculous or benign choriolympheocytic meningitis. Likewise, it may be confused with brain tumor, subarachnoid hemorrhage, brain abscess, encephalitis or subdural hematoma. The majority of cases pursue a slightly febrile course, but the temperature rarely exceeds 101° and is frequently normal. The pulse may be normal or slightly increased in frequency, but may fall to between 40 or 50.

Hematologic studies are of no value. A slight leukocytosis is common, but the white blood cell count is frequently normal. Polymorphonuclears usually predominate, but lymphocytes may be relatively increased. On some few occasions Torulae have been cultivated from the blood and urine.²⁰ In cases in which cutaneous or pulmonary involvement is present, the skin lesion or sputum may yield a positive culture.

The antemortem diagnosis of Torula meningitis can be made only by examination of the cerebrospinal fluid, and even the cerebrospinal fluid findings

TABLE I
Summary of All Reported Cases of Central Nervous System Torulosis
(According to the Schema of Levin)

	Levin 1937	Binford 1940	Beck-Voyten 1945	Arnold- Monberg 1949	Total
Sex of patient:					
Male	39	9	23	51	122
Female	20	4	13	13	50
Age distribution in years:					
Under 10	1	2	1	7	11
10-19	6	1	4	5	16
20-29	9	3	9	9	30
30-39	9	3	8	12	32
40-49	15	1	4	13	33
50-59	16	1	7	11	35
60-69	2	2	2	3	9
Not stated	2	0	0	4	6
Duration of illness in months:					
0-1	3	3	3	7	16
1	6	0	1	4	11
2	10	3	6	10	29
3	9	1	5	7	22
4	8	0	5	1	14
5	3	1	2	4	10
6	3	2	1	2	8
7	1	0	1	1	3
8	2	0	0	4	6
9	1	0	1	0	2
10-12	1	0	1	1	3
13-24	3	0	1	4	8
61-72	1	0	0	0	1
Unknown	4	0	7	17	28
Organs involved including the central nervous system:					
Lungs	9	4	7	21	41
Generalized	8	1	6	4	19
Kidney	2	2	8	7	19
Spleen	1	1	3	5	10
Adrenal glands	1	1	5	3	10
Abdominal nodes	1	0	3	1	5
Peribronchial nodes	1	0	1	2	4
Tonsil	3	0	0	0	3
Subcutaneous tissue	2	0	2	3	7
Skin	5	0	1	3	9
Central nervous system only	30	4	20	29	83
Bone	0	0	0	2	2
When diagnosed:					
Post mortem	23	8	6	17	54
Ante mortem	37	5	29	47	118
How diagnosed:					
Antemortem cultures only	10	4	26	24	64
Biopsy of the brain ante mortem	2	1	5	3	11
Postmortem histologic sections	22	0	4	14	40
Cultures and postmortem histologic sections	26	0	1	25	52

are inconstant. The spinal fluid is usually under increased pressure, opalescent and slightly yellow. The pressure may, however, be normal and the fluid may be clear and colorless. The cell count is usually elevated with a high lymphocyte count, although polymorphonuclears may predominate.

The spinal fluid sugar is usually significantly diminished and the chlorides may be likewise. The protein is almost always elevated. Before the diagnosis of *Torula meningitis* can be made, the organism must be identified in the cerebrospinal fluid either by direct microscopic examination or by culture. More frequently than not initial microscopic examination of the fluid discloses no *Torulae* and even the culture may be negative. It must be emphasized that one or more negative cultures do not exclude the possibility of torulosis. Not only must repeated cultures be taken, but the cultures must be incubated for a minimum period of one month. Perhaps the most disheartening situation exists when the growth of fungus on the culture medium is considered a contaminant and the culture is discarded.^{2, 60, 78} To make a clinical diagnosis of torulosis one must be at all times aware of the disease. Torulosis should be suspected whenever an unexplained cerebrospinal fluid pleocytosis is present.

It is interesting to note that, although Voyles and Beck in 1946 were able to collect only 108 cases from the literature, 64 cases, including five of the authors', have been reported since that time. It is also noteworthy that during the last decade the percentage of diagnoses made ante mortem has markedly increased (table 1). Obviously the incidence is far greater than the recognition of the disease; and the alleged rarity of the disease is in a large measure attributable to failure to make the diagnosis. It appears that the growing literature on the subject is bringing *Torula meningitis* to the attention of the clinician, thus increasing the frequency with which the diagnosis is made.

The diagnosis was made ante mortem in four of the five cases reported by the authors. In Case 1, the diagnosis was missed clinically because the disease was not suspected. In the remaining four cases, the possibility of the disease was suspected and the diagnosis made ante mortem.

DISCUSSION

The cases presented exhibit four interesting features: the long survival and absence of postmortem evidence of torulosis in Case 3, the coexisting systemic moniliasis in Case 5, the neurosurgical implications of the first three cases, and the therapeutic measures employed in all cases.

The known duration of torulosis in Case 3 was 38 months. By virtue of the autopsy findings, it is felt that a ventriculocisternostomy might have prolonged the patient's life. Although the eventual outcome of the disease is practically always death, there is a great variance in the severity and length of the clinical course between onset of initial symptoms and exitus. Occasional periods of remission have been noted. One to six months has been the usually recorded duration of the disease. Sixteen cases have been reported in which the total duration of the illness has been one month or less.^{54, 14, 90, 94, 71, 55, 74, 40, 22} On the other hand, the course may be greatly prolonged, one case being alive seven years and eight months after onset.⁷⁹ Other cases have

TABLE II
Analysis of Reported Cases Since Review of Voyles and Beck in 1945
(According to Schema of Binford)

Author	State Country	Age	Sex	Race	Duration Symptoms before Adm.	Cell Count in Spinal Fluid	Lympho- cytes in Spinal Fluid	Leuko- cytes in Blood	Diag- nosis Ante Mortem	Duration after Adm.	Autopsy	Torula in Organs in Addition to Brain	Remarks
Roger, Poursines, Pitot and Temple ²⁴	France	58	F	W	Un- known	80	80		No	3½ mos.	Yes		Diagnosis made post mortem. Two ventricular punctures performed ante mortem
Champion de Crespigny ¹⁴ Case 1	Australia	52	M	W	3 mos.		Predom.	11,500	Yes	10 wks.	Yes	Lungs	Diagnosis made by smear and culture of spinal fluid. Treat- ment: Potassium iodide, try- arsamide, hexamine and deep x-ray to brain and spine
Champion de Crespigny ¹⁴ Case 2	Australia	29	M	W	3 days	30	25	5,500	Yes	1 mo.	Yes	Lungs, adrenals, tracheo- broncho- pulmonary lymph gl., spleen, kidney, pancreas, prostate	Diagnosis made from blood culture. Treatment: Sulfapyridine. Death caused by leptomeningitis involving pia, arachnoid, choroid plexus
T. Costellano ¹⁹	Argentina	45	F	W	Un- known			10,800	Yes	2 mos.	Yes	Lungs	X-ray showed ulcerative dense lesion in rt. lung. Torula le- sion in rt. lung at autopsy. Diag. by smear of spinal fluid
Hagen ⁴⁰	N. Y.	36	M	W	7 days	64 189	57% 81	22,700	Yes	6 days	Yes		Diagnosis by smear and cul- ture of spinal fluid. Treat- ment: Intravenous and intra- thecal sulfathiazole
Swanson and Smith ³² Case 1	Ga.	49	F	W	1 yr.				No		Yes	Autopsy limited to brain	Tumor masses in rt. cerebellar hemisphere, left occipital lobe and rt. occipital lobe

TABLE II—Continued

Author	State or Country	Age	Sex	Race	Duration Symptoms before Adm.	Cell Count in Spinal Fluid	Lymphocytes in Spinal Fluid	Leukocytes in Blood	Diagnosis Ante Mortem	Duration after Adm.	Autopsy	Torula in Organs in Addition to Brain	Remarks
Swanson and Smith ¹⁶ Case 2	Ga.	36	M	W	2 yrs.	6 165			Yes	5 mos.	Yes	Lungs, spleen	Ventriculogram and cerebellar craniotomy revealed Torula granuloma, rt. cerebellar hemisphere. Cerebellar craniotomy repeated for regrowth of Torula granuloma. Treatment: potassium iodide, an autogenous vaccine. Spinal fluid cultures on readmission positive for Torula
Tinney and Schmidt ¹⁸ Case 1	Wisc.	32	M	W	15 days			9,000 16,000	Yes	2 mos.	Yes		Treatment: sulfadiazine, intrathecal tyrocidine. Coexistent pneumonia treated with sulfathiazole
Tinney and Schmidt ¹⁸ Case 2	Nebr.	23	M	W	1 mo.				No	1 wk.	Yes	Lungs, liver, spleen, adrenals, kidneys, prostate, testes, thyroid	Hodgkin's disease for 5 yrs. Treated with x-ray before and after admission
Tinney and Schmidt ¹⁸ Case 3	La.	25	M	W	3½ mos.		118		Yes	1 mo. (disch.)		Lungs	Diagnosed by spinal fluid culture. Treatment: Intrathecal tyrocidine, sulfathiazole. Asymptomatic 8 mos. after discharge. Culture of fluid obtained at bronchoscopy yielded Torula
Cohen ¹⁷	N. Y.	36	F	W	2 mos.	65 298	77 95		Yes	4 mos.	Yes	Culture of urine yielded Torula	Diagnosed by spinal fluid culture. Coexistent Hodgkin's disease. Treatment: Sulfadiazine, trephination for ventricular drainage. Developed streptococcus meningitis which was treated with intrathecal methylosaniline chloride

TABLE II—Continued

Author	State or Country	Age	Sex	Race	Duration Symptoms before Adm.	Cell Count in Spinal Fluid	Lymphocytes in Spinal Fluid	Leukocytes in Blood	Diagnosis Mortem	Duration Adm.	Autopsy	Torula in Organs in Addition to Brain	Remarks
Geevers, Carter, Neuberger and Schmidt ²⁸	Col.	53	F	W	Unknown	181			Yes	3 mos.	Yes	Lungs	Diagnosed by smear of spinal fluid and inoculation of guinea pig and mouse. Treatment: Sulfadiazine, iodides and acriflavine HCl
Jones and Klinck ⁴⁰	N. Y.	50	M	W	5 days	64	53	9,400	Yes	41 days	Yes	Spinal cord, kidneys	Diagnosed by spinal fluid culture. Treatment: Iodides, sulfadiazine, gentian violet, thymol. Blood cultures at autopsy, positive for Torula
Dormer, Friedlander, Wiles and Simpson ³⁰	South Africa	12	M	C	4 mos.			18,200	Yes	1 mo. (disch.)		Lungs	Post-operative meningitis following rt. upper pulmonary lobectomy. Treatment: Sulfadiazine and potassium iodide. Guinea pig inoculated with spinal fluid showed Torula lesions
Piper ⁷⁴	Australia	58	M	W	8 days	1,800 (polys)		43,150	Yes	3 days			Known period of illness, 11 days. Hemolytic streptococcus and <i>Cryptococcus neoformans</i> cultured from spinal fluid.
Allen and Lowbeer ²	Okla.	34	F	W	2 wks.	350	Predom.	—	No	2 mos.	Yes		Pre-mortem culture of spinal fluid showed extensive growth of fungus which was considered contaminant by technician and discarded. Authors feel that the fungus entered the body by way of perirectal fistula and abscess of rectal ulcer

TABLE II—Continued

Author	State or Country	Age	Sex	Race	Duration Symptoms before Adm.	Cell Count in Spinal Fluid	Lymphocytes in Spinal Fluid	Leukocytes in Blood	Diagnosis Aut. or Mortem	Duration after Adm.	Autopsy	Torula in Organ in Addition to Brain	Remarks
Cox and Tolhurst ¹⁹ Case 1	Australia	47	F	W	1 mo.	67	40		Yes	5 mos.	No	Subcutaneous tissue of thigh	Torulosis proved only in lesion on thigh. X-ray showed area of dullness in middle zone of left lung. Although spinal fluid cultures neg., subtemporal decompression performed for relief of headache. Died 6 mos. after onset
Cox and Tolhurst ¹⁹ Case 2	Australia	41	F	W	19 days	20 301	19 30		No	15 days	Yes	Other organs not microscopically examined	Period of incubation of spinal fluid cultures unknown; reported as neg. Pneumoencephalogram performed.
Cox and Tolhurst ¹⁹ Case 3	Australia	28	F	W	6½ mos.	110 82	45 14		Yes	1 mo.	Yes		Diagnosed by spinal fluid culture. Blood and spinal fluid Wassermann positive
Cox and Tolhurst ¹⁹ Case 4	Australia	44	M	W	24 wks.	335 449 140	157 24 100		Yes	16 days	Yes	Lung	Ventriculogram performed and thorotrast injected into lateral ventricles. Treatment: Colloid copper and sodium thiosulfate
Cox and Tolhurst ¹⁹ Case 5	Australia	7	M	W	5 wks.	41 50	40 46		Yes	24 mos.	Yes	Lungs	Diagnosed by spinal fluid cultures. X-ray of chest showed pulmonary fibrosis with small nodules suggestive of miliary TB. Operative procedures: ventriculogram, post. fossa exploration, rt. occip. craniotomy and incision of tentorium cerebelli

TABLE II—Continued

Author	State or Country	Age	Sex	Race	Duration Symptoms before Adm.	Cell Count in Cerebral Fluid	Lymphocytes in Cerebral Fluid	Leukocytes in Blood	Diagnosis Ante Mortem	Duration after Adm.	Autopsy	Torula in Organs in Addition to Brain	Remarks
Cox and Tolhurst ¹⁰ Case 6	Australia	30	M	W	7 wks.	142 220	25 126 56	10,000	Yes	21 days	Yes		Diagnosed by smear and culture of spinal fluid. Ventriculogram performed
Cox and Tolhurst ¹⁰ Case 7	Australia	62	M	W					No	2 days	Yes	Lung	Probably coexistent Hodgkin's disease. Predominant Torula infestation in lung
Cox and Tolhurst ¹⁰ Case 8	Australia	49	M	W	12 wks.	150 180 1,200 600 400 120 84 100 100	Predom. Predom. Predom. Predom. Predom. Predom. Predom. Predom.		Yes	5 mos.	No	Lungs	Diagnosed by smear and culture of spinal fluid. Coexistent tuberculosis and mucocoele of left frontal sinus. Treatment: M & B 693, and an autogenous vaccine
Cox and Tolhurst ¹⁰ Case 9	Australia	43	F	W	10 days	380 250 500 300 280 240 24 156 67	Predom. Predom. Predom. Predom. Predom. Predom. Predom.		Yes	3 yrs. 2 mos.	No	Lungs	Subarachnoid hemorrhage originally suspected. Treatment: M & B 693 and a Torula vaccine. Patch of consolidation in base of rt. lung. Organism proved resistant to penicillin
Cox and Tolhurst ¹⁰ Case 10	Australia	61	M	W	4-6 wks.	80	Predom.		Yes	36 days	Yes	Lung	Suspected of having left temporal or occip. tumor with uncinate herniation. Gelatinous fluid containing Torula aspirated at time of ventriculography

TABLE II—Continued

Author	State Country	Age	Sex	Race	Duration Symptoms before Adm.	Cell Count in Spinal Fluid	Lympho- cytes in Spinal Fluid	Leuko- cytes in Blood	Diag- nosis After Mortem	Dura- tion after Adm.	Autopsy	Torula in Organs in Brain	Remarks
Cox and Tolhurst ²⁹ Case 11	Australia	46	M		W	2 mos.	160 300 52 188 200	Predom. 50% — Predom. Predom.		Yes	Still living March, 1945	No	Diagnosed by spinal fluid cul- ture; apparently had spon- taneous remission. Hyper- thermic treatment attempted with TAB vaccine but satis- factory temperature not ob- tained. Alive 2 yrs. 7 mos. after onset
Cox and Tolhurst ²⁹ Case 12	Australia	58	M		W	9 wks.	100 152 200 104 152	Predom. — Predom. Predom. Predom.		Yes	3 mos.	Yes	Lung Diagnosed by smear and cul- ture of spinal fluid. Treat- ment: M & B 693, autogenous vaccine and sulfapyridine
Cox and Tolhurst ²⁹ Case 13	Australia	52	M		W	2 yrs.	180	Predom.			1 mo.		Bilateral frontal trephines per- formed since subdural hema- toma suspected. Treatment: Sulfathiazole. Alive two years after onset
Lewin and Roux ²⁸ Case 1	South Africa		M		C		12		Yes	11 days	Yes		Treatment: M & B 693, po- tassium iodide
Lewin and Roux ²⁸ Case 2	South Africa		M		W	8 days	49 96			Disch. after 6 mos.			Diagnosed by spinal fluid cul- ture. Treatment: Sulfapyri- dine, intramuscular and intra- theal penicillin, potassium iodide. Eleven mos. after on- set spinal fluid showed 24 lymphs, no Torula. Patient asymptomatic
Lewin and Roux ²⁸ Case 3	South Africa		M		C	2 wks.	28		No	2 mos.	Yes	Lung	Treatment: Sulfadiazine, in- tramuscular and intrathecal penicillin, potassium iodide

TABLE II—Continued

Author	State or Country	Age	Sex	Race	Duration of symptoms before Adm.	Cell count in Spinal Fluid	Lymphocytes in Spinal Fluid	Leukocytes in Blood	Diagnosis after Autopsy or Mortem	Data after Adm.	Autopsy	Tumors in Organs in Addition to Brain	Remarks
Lewin and Roux ²⁴ Case 4	South Africa		M	W	2 mos.		14 53		Yes	3 mos.	Yes		Patient became blind 2 mos. after onset of symptoms. Treatment: Sulfadiazine, potassium iodide
Flinn, Hooker and Scott ²⁵	Del.	49	M	C	6 mos.	300 500		7,200 5,200		9 mos.	Yes	Lung, stomach, ileum, colon	Diagnosed by smear and culture of spinal fluid and fluid aspirated from lung mass. Treatment: Sulfathiazole, sulfadiazine, potassium iodide, antimony and potassium tartrate
Hamilton and Tyler ²⁶	Calif.	24	F	W	Unknown	180	160	15,000 8,600 13,400	Yes	2 mos.	Yes	Lungs	Cerebral symptoms appeared 6 mos. after pulmonary symptoms; ventriculogram performed. Treatment: Sulfathiazole, potassium iodide, intramuscular and intrathecal penicillin
Kramer, Small Hewitt and Deness ²⁷	Africa	32	M	C	3 wks.	Norm.				2 yrs. 1 mo.		Subcutaneous tissue thigh, tumor left orbit	Meningeal tumor and tumor of left orbit removed after ventriculogram and left frontal craniotomy. Histologically, lesions found to be due to Torula. Treatment: Massive doses of iodides
Hamilton and Thompson ²⁸	La.	6	M	C	2 wks.	320	30%	13,120	Yes			Lungs	Diagnosed by culture of spinal fluid and sputum. Pneumoencephalogram and ventriculogram performed. Treatment: Intramuscular and intrathecal penicillin. Lack of clinical improvement but decrease in number of Torula colonies following treatment

TABLE II—Continued

Author	State or Country	Age	Sex	Race	Duration of Symptoms before Adm.	Cell Count in Spinal Fluid	Lymphocytes in Spinal Fluid	Leukocytes in Blood	Diagnosis after Mortem	Duration after Adm.	Autopsy	Torula in Addition to Brain	Remarks
Riveros, Boggino and Mayors ⁴⁰	Paraguay	54	M	W	3 mos.				Yes	Still living			Subcutaneous tumors of neck, scalp and thorax removed. Histologic sections of neck tumor revealed torulosis. Treatment: Sulfathiazole and penicillin. Spinal fluid not investigated although patient complained of headache. Alive 3 mos. after onset
Mezey and Fowler ⁴¹	Conn.	38	F	W	9 mos. 5 days		5	5,950	Yes	Disch. after 3 mos.			Diagnosed by spinal fluid culture. Treatment: continuous IV 5% alcohol, potassium iodide, oxophenarsine HCl, methylene blue, antimony compounds. Alive 1 yr. after onset
Hassin ⁴² Case 1	Ill.	49	M	W	5 mos.	16		22,000	No	2 yrs.	Yes		Exploratory trephines performed; well encapsulated tumor; size of hen's egg in left cerebellar hemisphere containing Torula
Hassin ⁴² Case 2	Ill.	46	M		2 mos.			6,700	No	2 wks.	Yes		Exploratory trephines performed. Brain and spinal cord affected
Mider, Smith and Bray ⁴³	Va.	12	M	C	3 mos.			2,400	No	11 days	Yes	Lymph nodes	Cocurrent infection with <i>Histioplasma capsulatum</i>
Greening and Menville ⁴⁴ Case 1	La.	52	M	C		150	30%	8,150	Yes	2 mos.	No		Diagnosed by smear and culture of spinal fluid and sputum. Treatment: Sulfadiazine and potassium iodide

TABLE II—Continued

Author	State of Country	Age	Sex	Race	Duration of Symptoms before Adm.	Cell count in Spinal Fluid	Lymphocytes in Spinal Fluid	Leukocytes in Blood	Diagnosis Ante Mortem	Duration after Adm.	Autopsy	Torula in Organ in Addition to Brain	Remarks
Greening and Menville ²⁹ Case 2	La.	24	M	C				11,400	Yes	10 mos.		Lungs	Torulosis confined to the lungs. Diagnosis made by smear and culture of pleural fluid. Treatment: Sulfadiazine, penicillin, potassium iodide, gentian violet, x-ray to lung. No cerebral symptoms in 1 yr. 4 mos.
Greening and Menville ²⁹ Case 3	La.	25	M	W	6 wks.	236		9,700	Yes			Lungs	Diagnosed by smear and culture of spinal fluid and material obtained from bronchoscopy. Treatment: Intramuscular and intrathecal penicillin, intrathecal tyrocidin, sulfathiazole. Alive after 4 yrs.
Greening and Menville ²⁹ Case 4	La.	6	M	C	2 wks.	300		13,120	Yes	2 mos.	No		Injected spinal fluid; killed rat in 3 days. Diagnosis by smear and culture of spinal fluid. Treatment: Intramuscular and intrathecal penicillin, sulfadiazine, potassium iodide
Debre et al. ²⁸	France	12	M	W	Unknown			4,300	Yes	2 wks.	Yes		Coexistent Hodgkin's disease. Diagnosis by spinal fluid culture. Torulosis not suspected until cerebral symptoms developed several weeks before death

TABLE II—Continued

Author	State or Country	Age	Sex	Race	Duration of Symptoms before Adm.	Cell Count in Spinal Fluid	Lymphocytes in Spinal Fluid	Leukocytes in Blood	Diagnosis at Mortem	Duration of Life after Adm.	Autopsy	Tumors in Organ in Addition to Brain	Remarks
Torrey ¹⁸	Calif.	42	M	W	Unknown			22,250		Alive 6 mos.		Skin	Cutaneous torulosis with no evidence of involvement elsewhere. A seborrheic eczema had been present for 12 yrs. prior to admission. Coexistent Hodgkin's disease, squamous cell epithelioma. Alive 6 mos. after admission and 1 mo. after diagnosis
Jesse ¹⁷	Calif.	24	M	Y	2 wks.			Norm.	Yes	Alive after 4 mos.		Bone	First reported case of torulosis of bone. X-ray of chest showed hazy and patchy infiltration most marked in right lung field. Right inferior pubic ramus, the involved area, removed; treated with penicillin and sulfadiazine. Asymptomatic 4 mos. after onset
Cloward ¹⁶	Hawaii	5½	M	Y	1 wk.	450	33%	21,750	Yes	28 days	Yes		Diagnosed by smear and culture of spinal fluid. Exploratory trephination for brain abscess negative. Pneumoencephalogram performed
Magarey and Denton ¹⁴	England	60	M	W	10 wks.	25	66 1 95%	Norm.	No	4 mos.	Yes		Thought to be either a cerebral tuberculoma or tuberculous meningitis. The possibility of torulosis was not considered
Neuhauser and Tucker ¹⁵ Case 1	Mass.	7 wks.	M	W	7 wks.		9	12,000	No	23 days	Yes		X-ray of skull showed numerous shadows of calcification in frontal region. At autopsy two large bilaterally symmetrical cysts in cerebral hemispheres noted along with calcium deposition in cortex and meninges

TABLE II—Continued

Author	State or Country	Age	Sex	Race	Duration of Symptoms before Adm.	Cell Count in Spinal Fluid	Lymphocytes in Spinal Fluid	Leukocytes in Blood	Diagnosis Ante Mortem	Duration after Adm.	Autopsy	Torula in Organs in Addition to Brain	Remarks
Neuhauser and Tucker ⁷¹ Case 2	Mass.	19 days	M		W	19 days		12,800	No	4 days	Yes	Spleen, liver, kidneys, bone	X-ray of skull showed confluent punctate calcification. Jaundiced since birth. At autopsy marked hydrocephalus and atrophy of brain; Torula involved bone
Neuhauser and Tucker ⁷¹ Case 3	Mass.	24 wks	M			4 days		4,600	No	10 days	Yes		X-ray of skull showed hazy intracranial calcification. At autopsy marked hydrocephalus and atrophy with extensive calcification within granulomatous lesion
O'Neill, Newcomb and Nielsen ⁷²		49	M		W	2 wks.	10,000	13,050	Yes	8 mos. (disch.)			Improvement following treatment with intrathecal and intramuscular penicillin, sulfadiazine and autogenous vaccines
Goldberg ²⁷	Tenn.	25	M		W	6 mos.	305	9,950	Yes	8 mos. (disch.)			Spinal fluid fixation against lymphocytic chorio-meningitis. Treatment: atabrine, sulfadiazine and penicillin
Moody ²⁷	Calif.	38	M		W	1-2		27,000	No	1 mo.	Yes	Lungs	Central nervous system not examined. Asphyxiated by Torula granuloma in tracheo-bronchial tree. Treatment: Penicillin and sulfadiazine. Diagnosis made post mortem
Dorner and Scher ²⁷	South Africa	17	M		W	6 wks.			Yes	1 mo.	No	Lung	Diagnosed by aspiration biopsy of lung. Spinal fluid not cultured. Treatment: KI, lipiodol

TABLE II—Continued

Author	State or Country	Age	Sex	Race	Duration of Symptoms before Adm.	Cell Count in Spinal Fluid	Lymphocytes in Spinal Fluid	Leukocytes in Blood	Diagnosis Ante Mortem	Duration after Adm.	Autopsy	Torula in Organs in Addition to Brain	Remarks
Sosa and Sotelo ¹⁰	Uruguay	43	M	W	Unknown				No	48 hrs.	Yes	Kidneys	Admitted with craniocerebral injury; died 48 hrs. later. Torula lesions found in kidneys at autopsy. Spinal fluid not cultured
Mosberg and Arnold Case 1	Md.	51	M	W	6 mos.	157	87%	8,650	No	2 mos.	Yes	Adrenals	Illness of 8 mos. duration. History of benign lymphocytic choriomeningitis 15 mos. prior to death. Treatment: Sulfanilamide. Disease not suspected
Mosberg and Arnold Case 2	Pa.	34	M	W	7 wks.	441	95	8,700	Yes	2 wks.	Yes		Frontal lobe tumor suspect. Ventriculogram negative. Treatment: Furacin. At autopsy, ischemic necrosis of adenohipophysis
Mosberg and Arnold Case 3	Md.	36	F	W	3 yrs.	180	82	7,300	Yes	38 mos.	Yes		Duration 38 mos. Treatment: Iodides, sulfadiazine, streptomycin, penicillin, typhoid fever, diazepam, alkalization. No evidence of torulosis at autopsy
Mosberg and Arnold Case 4	Md.	37	M	W	7 days	396	92	9,950	Yes	7 mos.	Yes		Remission after alkalization therapy and penicillin. Recurrence of symptoms 7 mos. after onset. Autopsy showed primary ependymitis with pleksitis and marked internal hydrocephalus
Mosberg and Arnold Case 5	Md.	18	M	W	1 yr.	706	68	13,250	Yes	3 mos.	Yes		Treatment: Streptomycin, alkalization. Prolonged hyperpyrexia attempted. Autopsy showed coexistent moniliasis

been reported as surviving seven years,¹⁰² five and one-half years,⁵⁴ four years,²³ etc. Cox and Tolhurst²⁰ feel that strains of *Torula histolytica* probably vary in virulence. In this connection, Warvi and Rawson¹⁰⁴ state: "If one judges by the case reports in the literature, the demonstration of organisms by culture is more difficult in cases in which the infection is of longer duration." Skinner et al.⁸⁶ have stated that following intracerebral injection of suspension of the organism, mice die within five to 15 days depending upon the virulence and dosage of the strain. An attempt is made in table 3 to correlate the laboratory studies in the five cases with the duration of illness in each case.

TABLE III
Laboratory Data in Cases Presented in This Report

No. Case	White Blood Cells	Sed. Rate	WBC in Spinal Fluid	% Lymphocytes in Spinal Fluid	Spinal Fluid Sugar	Smear of Spinal Fluid	Days Incubation on Sabouraud's Medium Before Culture Positive	Days Survival of Mice Following Intracerebral Inoculation of Torula Culture	Duration of Illness in Patient
1	8,650		100	48	14	Neg.	None	None	8 months
2	8,700	34	441	95	33	Torula	1	12	9 weeks
3	7,300	22	180	82	18	Torula	6	22	38 months
4	9,950	0	396	92	53	Torula	25	15	7 months
5	13,250	18	706	68	17.5	Torula	2	10	3 months

Although torulosis has been associated with many other diseases, there is no recorded case of torulosis associated with moniliasis. The disease most frequently reported as coexisting with torulosis is Hodgkin's disease.^{98, 17, 20, 23, 98} Fitchett and Weidman,²⁸ as well as Burger and Morton,¹² have called attention to the fact that torulosis produces granulomatous lesions resembling those of Hodgkin's. They postulate that perhaps some of the cases were misdiagnosed Hodgkin's disease before the diagnosis of torulosis was established. Other conditions mentioned in the literature in association with torulosis are chronic lymphatic leukemia,⁶⁰ diabetes mellitus,⁶⁰ pregnancy,⁹⁴ verrucous endocarditis,⁹⁴ pyelonephritis,⁹⁴ lead encephalopathy,¹² and histoplasmosis.⁶⁶ Moniliasis has been reported as invading the central nervous system,^{65, 85, 91, 98} but never previously in association with torulosis.

Although the disease usually takes the form of a meningitis or meningo-encephalitis, signs of systemic infection may be predominant. In most instances the respiratory tract has been considered the route by which the fungus enters the body. The cryptococcus has been reported as gaining entrance by way of the gastrointestinal tract,² tonsils,³³ and even through a laceration in the skin.⁴⁸ Wade and Stevenson¹⁰³ have presented evidence that the disease is a true septicemia. On the other hand, cases have been recorded in which the disease is localized. In these reports the infection has been limited to the nasopharynx,⁴⁸ tongue,⁵¹ pubic bone,⁴⁷ muscles of the ver-

tebral column,¹¹ lungs,^{19, 29, 27, 67} subcutaneous tissues,^{12, 20, 25, 80} and pelvic and inguinal region.⁷⁰ Cutaneous torulosis has also been described.^{68, 76, 98, 105, 106}

Five cases of torulosis in the form of a localized tumor of the central nervous system have been reported. Four of these were intracranial tumors,^{24, 45, 53, 93} and the other a tumor of the spinal cord.⁸⁷ Each of these lesions acted as a space occupying mass and surgical removal was attempted in three cases.

In surveying the 64 cases analyzed in this review, it was found that ventriculography was performed on eight occasions.^{93, 20, 43, 42, 53} Five of the patients had exploratory trephines.^{16, 20, 45} The posterior cranial fossa was explored in two of the patients,^{20, 93} and the anterior fossa in one.⁵³ Other neurosurgical procedures were subtemporal decompression for relief of headache,²⁰ trephination for ventricular drainage,¹⁷ and right occipital craniotomy with incision of tentorium cerebelli in order to reduce an uncinat hernia.²⁰ In our Case 3 ventriculocisternostomy was contemplated but was not carried out. The neurosurgical lesions suspected in this group of patients included: subdural hematoma,²⁰ subarachnoid hemorrhage,²⁰ brain abscess,¹⁶ frontal lobe tumor,⁵³ temporal lobe tumor,²⁰ occipital lobe tumor,²⁰ cerebellar tumor,^{93, 20} and uncinat hernia.²⁰

By and large, the therapeutic problems in torula meningitis are medical rather than surgical. The advent of chemotherapeutic and antibiotic agents in recent years, together with the increased incidence of ante mortem diagnosis of torulosis, has resulted in the employment of many therapeutic agents against this disease. It is felt that an analysis of the recorded experiences of those who have endeavored to treat torulosis should be made. These data are presented in table 4.

It would appear from reviewing this table that any encouragement provided by an apparent response to a drug is in most cases nullified by an equally discouraging response when the same drug is employed on another patient. Torula antigen (Kreuger) employed by Reeves, Butt and Hammack in their Case 4,⁷⁹ and by O'Neill et al.,⁷³ may be of some value. Sulfa drugs and penicillin are apparently of little value. The report of Mezey and Fowler⁶⁴ is of extreme interest since their patient is still alive and, further, since their method of treatment has been employed in no other reported case. By virtue of recent experimental *in vitro* studies,³ however, it is felt that perhaps their use of oxophenarsine HCl (mapharsen) was of more significance than the continuous intravenous 5 per cent alcohol which was used in treating this case. The consideration of therapy in its entirety, however, is modified by the fact that Binford's patient,¹⁰ alive and working 23 months after the onset of central nervous system torulosis, had received no therapy other than aspirin and lumbar punctures.

Each of the five cases here reported received some therapeutic agent, although in Case 1 the diagnosis was not established ante mortem. Case 1 showed no response to sulfanilamide. The clinical course of Case 2 was not altered by Furacin. Many therapeutic measures were employed in Case 3,

TABLE IV
Review of Therapeutic Measures Employed

Author	Therapeutic Agent	Remarks
Reale ⁷⁸ Toone ⁹⁷	Iodides Iodides	Results poor Apparent cure resulted, but two years later symptoms re- curred and spinal fluid cul- tures became positive
Shapiro and Neal ⁸⁸ Case 1	Iodides intrathecally	Results poor
Shapiro and Neal ⁸⁶ Case 2	Colloidal silver, immune rab- bit's serum intraspinally	No beneficial result
Lynch and Rose ⁸⁸ Warvi and Rawson ¹⁰⁰	Iodides intrathecally Roentgen-rays	Results poor Coexistent Hodgkin's disease. Remission occurred twice, but died 18 mos. after onset of neurologic symptoms
Reeves, Butt and Hamack ⁷⁹ Case 4	Azossulfamide, sulfapyridine, Torula antigen (Krueger), po- tassium iodide	Alive 7 yrs., 8 mos. after on- set. Frontal craniotomy sus- pecting brain abscess
Reeves, Butt and Hamack ⁷⁹ Case 5	Azossulfamide	Died 10 weeks after onset
Reeves, Butt and Hamack ⁷⁹ Case 6	Sulfanilamide, sulfapyridine	Died 3 months after onset
Nichols ⁷² Goldberg ³⁸	Acridavine intrathecally Massive doses, vitamin D	No beneficial results Dramatic improvement but recurrence and death five months later
Sampson and Farren ⁹³ Marshall and Teed ⁶²	Sulfapyridine Bilateral mastoidectomy, sul- fadiazine, potassium iodide	Died six months after onset Apparent cure (followed for five months)
Hamilton and Thompson ⁴² Case 1	Sulfathiazole, intrathecal tyrocidin	Patient living but has symp- toms 32 months after onset
Hamilton and Thompson ⁴² Case 2	Sulfadiazine, penicillin	No apparent effect on the course of the disease. Lack of clinical improvement, but decrease in number of colonies
Stone and Sturdivant ⁷²	Gold sodium thiosulfate intra- venously. Gentian violet intra- venously and intraspinally, hexamethylamine intraven- ously	Patient died seven and a half weeks from inception of the illness.
Lynch and Rose ⁸⁸	20 c.c. 1:1,000 mercurochrome intraspinally	Patient died 16 hours after injection
Stone and Sturdivant ⁹² Voyles and Beck ¹⁰² Case 3	X-ray to skull Potassium iodide, sulfadiazine	No response Died 10 weeks after onset
Voyles and Beck ¹⁰² Case 4	Penicillin, intrathecal penicil- lin sulfadiazine	Appeared to respond initially to sulfadiazine; no apparent response to penicillin; alive seven years after onset
Champion de Crespigny ⁴⁴ Case 1	Potassium iodide, trypanam- ide, hexamine, deep x-ray to brain and spine	Dead five and one-half months after onset
Champion de Crespigny ⁴⁴ Case 2	Sulfapyridine	Dead one month after onset
Hagen ⁶⁹	Intravenous and intrathecal sulfathiazole	Duration of illness two weeks
Swanson and Smith ⁹¹ Case 2	Potassium iodide, autogenous vaccine	Duration of illness two years, five months
Tinney and Schmidt ⁸⁶ Case 1	Sulfadiazine, intrathecal tyro- cidine	Duration of illness two and one-half months
Tinney and Schmidt ⁸⁶ Case 3	Sulfathiazole, intrathecal tyro- cidine	Asymptomatic one year after onset
Cohen ¹⁷ Geevers, Carter, Neuberger and Schmidt ⁸⁴	Sulfadiazine Sulfadiazine, iodides, acridav- ine HCl	Duration of illness six months Dead after three months hospitalization

TABLE IV—Continued

Author	Therapeutic Agent	Remarks
Jones and Klinck ⁴⁰	Iodides, sulfadiazine, gentian violet, thymol	Dead 46 days after onset
Dormer, Friedlander, Wiles and Simpson ²⁶	Sulfadiazine, potassium iodide	Alive five months after onset
Cox and Tolhurst ²⁷ Case 4	Colloidal copper, sodium thio-sulfate	Dead one month after onset
Cox and Tolhurst ²⁷ Case 8	M & B 693, autogenous vaccine	Dead eight months after onset
Cox and Tolhurst ²⁷ Case 9	M & B 693, autogenous vaccine	Dead after three years, two months. Organism proved resistant to penicillin
Cox and Tolhurst ²⁷ Case 11	Unsatisfactory attempt at hyperthermic treatment with TAB vaccine	Alive two years, seven months after onset
Cox and Tolhurst ²⁷ Case 12	M & B 693, autogenous vaccine, sulfapyridine	Dead five months after onset
Cox and Tolhurst ²⁷ Case 13	Sulfathiazole	Alive two years after onset
Lewin and Roux ⁴⁶ Case 1	M & B 693, potassium iodide	Died after 11 days hospitalization
Lewin and Roux ⁴⁶ Case 2	Sulfapyridine, intrathecal penicillin, potassium iodide	Asymptomatic with negative spinal fluid cultures 11 months after onset
Lewin and Roux ⁴⁶ Case 3	Sulfadiazine, intrathecal penicillin, potassium iodide	Dead after illness of two and one-half months
Lewin and Roux ⁴⁶ Case 4	Sulfadiazine, potassium iodide	Dead after illness of five months
Flinn, Hooker and Scott ²⁹	Sulfathiazole, sulfadiazine, potassium iodide, antimony, potassium tartrate	Dead 15 months after onset
Hamilton and Tyler ⁴³	Sulfathiazole, potassium iodide, intrathecal penicillin	Dead after two months hospitalization
Krainer, Small, Hewlitt and Deness ³⁴	Iodides	Alive two years, one month hospitalization
Hamilton and Thompson ⁴²	Intrathecal penicillin	Lack of clinical improvement, but decrease in number of Torula colonies following treatment
Riveros, Boggino and Mayor ⁴⁹	Sulfathiazole	Subcutaneous tumors; spinal fluid not investigated but complains of headache. Alive three months after onset
Mezey and Fowler ⁶¹	Continuous intravenous 5% alcohol, potassium iodide, oxophenarsine HCl, methylene blue, antimony comp.	Alive one year after onset
Greening and Menville ²⁸ Case 1	Sulfadiazine, potassium iodide	Dead after two months' hospitalization
Greening and Menville ²⁸ Case 2	Sulfadiazine, penicillin, potassium iodide, gentian violet, x-ray to lung	Torulosis confined to lungs; no cerebral symptoms in one year, four months
Greening and Menville ²⁸ Case 3	Intrathecal penicillin, intrathecal tyrocidine, sulfathiazole	Alive four years after onset
Greening and Menville ²⁸ Case 4	Intrathecal penicillin, sulfadiazine, potassium iodide	Dead two and one-half months after onset
O'Neill, Newcomb and Nielsen ²³	Intrathecal and intramuscular penicillin, sulfadiazine, autogenous vaccines	Discharged markedly improved clinically after eight months' hospitalization
Goldberg ²²	Atabrine, sulfadiazine and penicillin	Alive after 14 months' illness, but spinal fluid cultures positive. These drugs did not affect course of disease
Moody ⁶⁷	Penicillin and sulfadiazine	Drugs had no effect on course of disease. Died after three months' illness
Dormer and Scher ²⁷	KI, lipidol (irrigation of pulmonary granuloma)	Drugs had no effect on course of disease. Died after 10 weeks' illness

including typhoid vaccine fever, and intramuscular and intrathecal penicillin and streptomycin. It is impossible to state which, if any, of these measures affected the course of the disease, but the patient appeared to improve clinically following the institution of alkalization therapy. Case 4 had a remission following a course of alkalization therapy, only to have his symptoms return and his spinal fluid cultures become positive several months later. Streptomycin and alkalization therapy failed to alter the course of the disease in Case 5. In the latter case moniliasis was associated with torulosis. Prolonged hyperpyrexia was unsuccessfully attempted in this case.

Despite the encouraging experimental studies of Beck and Muntz,⁶ it is not logical to assume that streptomycin would be of value since the *Cryptococcus* is known to produce acid,^{18, 84} and Murray and Finland⁸⁹ have stated: "There is in vitro and clinical evidence to show that an increase in the acidity of the medium has resulted in an appreciable and sometimes marked increase in the concentration of streptomycin required to inhibit the growth of various bacteria." In the two cases in which it was employed, streptomycin had no effect on the progress of the disease. Although prolonged hyperthermia appears experimentally to affect the survival of *Cryptococcus neoformans*, Cox and Tolhurst²⁰ have observed that febrile cases of torulosis seem to succumb even more rapidly than those which are afebrile. They have also observed that even experimental animals, such as rabbits, with a high normal temperature, may develop torulosis. The hyperthermia was of insufficient duration in the two cases in which it was employed for any conclusions to be drawn.

CONCLUSIONS

1. Five cases of torulosis of the central nervous system are reported. One of these cases survived 38 months after the onset of symptoms and showed no evidence of torulosis at autopsy. Another of these cases was associated with moniliasis.
2. Including the five cases reported by the authors, 172 cases of torulosis have been reported to date.
3. Therapeutic agents which have been employed in the reported cases are analyzed. As yet, no method of treatment has proved effective.
4. The chief error in diagnosis is in "not thinking of the disease." The diagnosis will seldom be missed if routine cultures are made on Sabouraud's medium and observed for one month.
5. The disease may be confused with brain tumor, subarachnoid hemorrhage, subdural hematoma, brain abscess, encephalitis, and meningitis of pyogenic, luetic, tuberculous or virus origin.

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CASE REPORTS

ACHALASIA (CARDIOSPASM): REPORT OF A CASE WITH EXTREME AND UNUSUAL MANIFESTATIONS *

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ACHALASIA (cardiospasm) is not a rare condition. It is usually seen in the middle aged individual and is characterized clinically by symptoms of dysphagia, regurgitation of food and epigastric discomfort. The roentgenologic diagnosis of cardiospasm is dependent upon the findings of varying amounts of dilatation of the esophagus and a smooth conical narrowing of the sub-diaphragmatic portion, which obstructs the flow of ingested contrast medium to varying degrees. It is interesting to note that achalasia is occasionally mis-diagnosed as a mediastinal tumor or abscess.^{1,2}

We believe this case of achalasia to present certain unusual clinical and roentgenologic manifestations heretofore not reported in the literature, as hoarseness which disappeared on assuming the supine position and the extreme dilatation of the cervical component of the esophagus giving rise to the so-called "bull frog appearance."

CASE REPORT

A white woman, 75 years of age, was in good health until 35 years ago, at which time, while eating, she gasped for breath and eructated. Following this episode she noted recurrent attacks of sudden generalized thoracic compression and a feeling of abdominal distention. The sensation of thoracic tightness migrated downward into the epigastrium and up the left side of the sternum to terminate in the left side of the neck where it produced a tight, vise-like, smothering feeling causing her to gasp for breath. The attacks were not described as being particularly painful and were not accompanied by vomiting. They were not infrequently precipitated by emotional strain or nervous excitement and lasted from five minutes to two hours in duration. These attacks could be relieved or partially relieved by lying in the supine position and eructating, or could be terminated by the inhalation of aromatic spirits of ammonia or by the intramuscular administration of morphine sulfate (0.01 gm.). The patient had painless dysphagia only during the attacks. Following these episodes she developed hoarseness which disappeared on assuming the supine position. She occasionally expectorated considerable amounts of mucoid material but disclaimed any associated vomiting. Two years ago she noted the development of a mass in the left side of her neck during one of the attacks. The mass enlarged with coughing and straining and slowly increased in size. There had been a gradual weight loss from 190 to 115 pounds within the past two years with a 12 pound weight loss during the three weeks prior to admission.

On May 12, 1947, she developed a severe attack with bulging of the neck, hoarseness and painless dysphagia and was admitted to Temple University Hospital.

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Physical examination revealed an elderly white female appearing younger than her stated age of 75. She presented an anxious facies and appeared somewhat pale and emaciated. A smooth bilateral swelling was present at the base of the neck. On the left side it measured 7 cm. in diameter, was bounded superiorly by the horizontal ramus of the mandible, inferiorly by the clavicle, posteriorly by the anterior border of the sternocleidomastoid muscle, and medially by the trachea. This prominence was soft, fluctuant, non-pulsating, non-reducible, hyperresonant and upon palpation gave the impression of a cyst filled with air (figure 2). Auscultation over this area revealed tubular breathing but no bruits were heard. On coughing and straining the prominence enlarged so that its transverse diameter measured 10 cm.



FIG. 1.

FIG. 1. Appearance of the neck at rest.

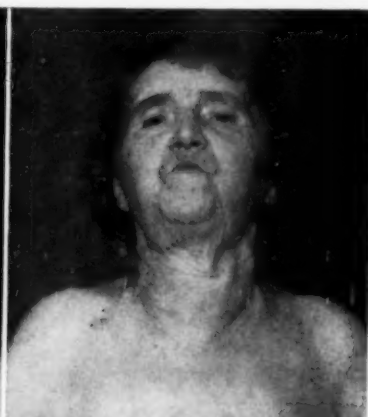


FIG. 2.

FIG. 2. Bulging of the anterior cervical spaces ("bull frog appearance") produced by increase of intrathoracic pressure.

It was not fixed nor adherent to the trachea. No evidence of a fistula was noted. On the right side a similar prominence measuring 5 cm. was present. This prominence also increased in size on coughing and had no external communication. Both prominences retracted on deep inspiration. There was no venous distention, no tracheal tug, no abnormal pulsations, no lymphadenopathy and the thyroid was not palpable. Over the right upper chest anteriorly the resonance was slightly impaired and the voice and breath sounds were diminished. No râles were heard. The cardiac impulse (PMI) was not visible or palpable. The heart was not enlarged to the left or right on percussion. The apical rate was 80, the sounds were distant, no murmurs were heard. The second aortic sound was louder than the second pulmonic sound. The abdomen was flat, relaxed and soft. No abnormal pulsations were seen and there was no tenderness or rigidity. The swallowing time was prolonged, the gastric gurgle being heard 22 seconds after water was swallowed. The tongue was smooth and red suggestive of a mild avitaminotic state. Slightly diminished pulsations of the dorsalis pedis bilaterally were demonstrated. All tendon reflexes were equal but hypo-active.

The blood count, urinalysis and the sedimentation rate were normal. The blood Wassermann reaction was negative. The sputum on culture revealed the usual throat

flora with a slight increase in *Streptococcus viridans* and hemolytic streptococci. The total blood serum protein was 6.2 gm. per 100 c.c. with a normal albumin-globulin ratio. The electrocardiogram was within normal limits (sinus rhythm with a rate of 65 per minute, P waves upright in all leads, P-R interval 0.14 second, QRS complexes upright, T-waves positive, precordial leads normal).

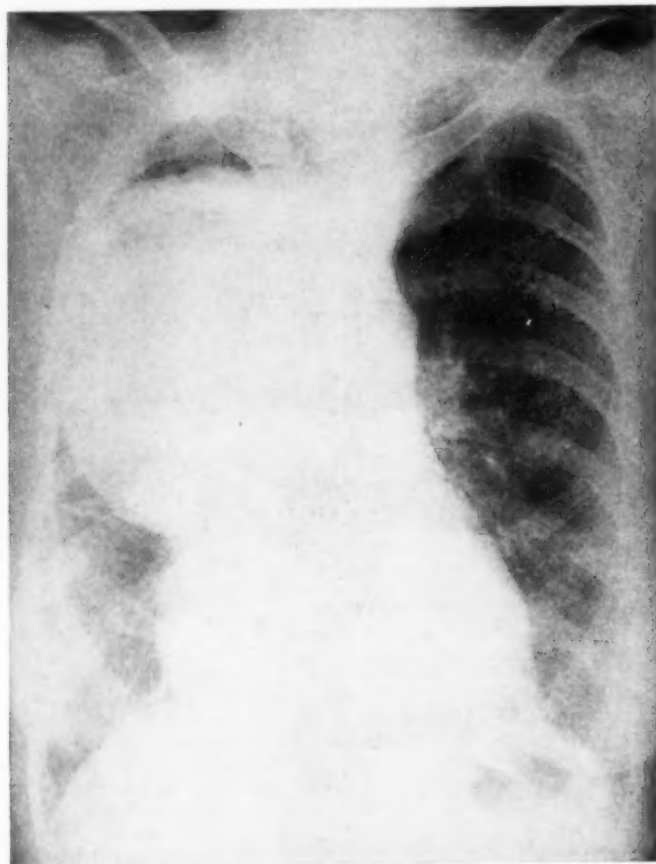


FIG. 3. Chest roentgenogram demonstrating the severe degree of esophageal dilatation and tortuosity.

Roentgenographic examination of the chest revealed that the esophagus was tremendously enlarged and tortuous in its entire length. The dilatation was maximal in the upper portion where the food passage contacted the right lateral chest wall (figure 3). As the dilated esophagus passed through the thoracic inlet it encroached upon the posterior tracheal wall, narrowing the trachea in this location. A large amount of mixed retained secretions and food debris was visible within the dilated

esophagus, and a fluid level was visualized in its upper thoracic portion. The cervical esophagus was similarly affected, appearing as a large air-filled structure measuring over eight centimeters in width, narrowing and displacing the trachea anteriorly (figure 4). An associated interesting feature of the dilatation of the upper food passage was the elevation and attenuation of the cricopharyngeus (figure 5). A barium sulfate-water mixture given by mouth mixed irregularly with the fluid content of the esophagus, but none of the radiopaque material was seen to pass through the



FIG. 4. Large, air-filled cervical esophagus encroaching upon narrowed trachea and larynx.

sub-diaphragmatic portion to enter the stomach. In the lower right chest, the right margin of the huge esophagus simulated the right heart border, but actually, the abnormally dilated esophagus obscured the cardiac border on the right side. The impression was severe cardiospasm of long duration.

Reexamination, following aspiration of the esophageal contents and the oral administration of a barium sulfate-water mixture, again demonstrated the severe degree of dilatation and tortuosity of the esophagus particularly in its upper thoracic portion (figure 6). The smooth, conical narrowing of the diaphragmatic portion of the lower end of the esophagus, typical of cardiospasm, was demonstrated. It was observed that only a partial obstruction to the flow of the barium sulfate-water mixture

existed, the contrast material entering the stomach slowly and intermittently during the course of the roentgenoscopic examination.

The esophagoscopic findings were those of advanced "cardiospasm." Despite preliminary lavage, a large accumulation of fluid and semi-solid food debris was encountered as the esophagoscope was introduced through the cricopharyngeal orifice; this was removed with the esophageal evacuator (C. L. Jackson). Although the



Fig. 5. Dilated air-filled cervical esophagus as visualized in the ventral projection.

esophageal walls seemed unusually redundant, the mucosal surface showed little inflammatory change and no ulceration was observed.

In this case, as in others of advanced cardiospasm, the simpler methods of dilatation (with Hurst mercury-filled bougies or the ordinary pneumatic dilator) were not feasible. Distortion and kinking of the tremendously dilated upper thoracic esophagus were such that these instruments could not be advanced to the hiatal level, despite maneuvers under roentgenoscopic guidance with the patient in various positions. Attempts with a pneumatic dilator adapted for introduction over a previously swallowed string of woven silk were somewhat more successful, but because of the nearly horizontal course of the terminal portion of the esophagus, the dilator could be advanced only part way to the optimum position for inflation.

The patient refused surgery and was advised to return to the Chevalier Jackson Bronchoscopic Clinic for treatment whenever necessary.



FIG. 6. Appearance of the esophagus following aspiration and the introduction of contrast medium.

SUMMARY

A case of achalasia (cardiospasm) is presented because of the following interesting features:

1. A "bull frog appearance," an increase of intrathoracic pressure causing bulging at the anterior cervical triangles, produced by the cervical component of a tremendously dilated and tortuous esophagus.
2. The symptomatic manifestations of:
 - a. Hoarseness which disappeared on assuming the supine position.
 - b. Occasional expectoration of a considerable amount of mucoid material with no history of vomiting per se.

- c. Gasping and eructation during attacks.
- d. Painless dysphagia only during the attacks.
- 3. A history of 35 years' duration.

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**MERCURIAL DIURETICS: SOME HAZARDS OF MERCUHYDRIN;
REPORT OF TWO CASES WITH ONE DEATH ***

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REPORTS of unfavorable reactions following the administration of mercurial diuretics are becoming more common. Kaufman¹ summarized 32 fatalities immediately following intravenous injection of mercurial diuretics. Molnar² reported a death following intraperitoneal administration (mercupurin). Kline and Seymour³ noted severe reactions following the administration of mercurin intravenously or by rectal suppository. Waife and Pratt⁴ observed a patient who died in anuria following prolonged administration of mercupurin. The injection precipitating the reaction had been given intramuscularly. This is the only previously reported fatality following intramuscular administration.

Reports of unfavorable systemic reactions to mercurhydrin have been limited to relatively few scattered observations. Modell, Gold and Clarke⁵ observed a patient who developed chills and fever about two hours after mercurhydrin given intravenously or intramuscularly but not after mercupurin given by both routes. Finkelstein and Smyth⁶ noted that a patient experienced precordial pain and anxiety immediately following the intravenous injection of 2 c.c. of mercurhydrin. This did not recur with subsequent injections. Gelfand⁷ noted palpitation, chills, fever and profuse sweating after intramuscular injection of mercurhydrin.

Manifestations of toxic reactions to mercurial diuretics have been adequately reviewed by DeGraff and Nadler⁸ in July 1942. References here will be limited chiefly to reports appearing since that date. Undesirable effects of mercurial diuretics may be grouped in three classes: (1) reactions attributable to diuresis with or without changes in the electrolyte balance, (2) reactions related to the mercury portion of the molecule and (3) reactions related to the organic structure of the specific mercurial compound.

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Reactions attributable to diuresis and changes in the electrolyte balance are due chiefly to chloride and/or sodium depletion and may be manifested by weakness, somnolence, muscle cramps, confusion, restlessness, excitement, coma and death. Tetany has occasionally developed.⁹ Grand mal epilepsy may be precipitated by this mechanism. Cerebral thrombosis following mercurial diuresis has been attributed to a decrease in blood pressure incident to decreased blood volume.¹⁰ Batterman, DeGraff and Shorr¹¹ considered the most common untoward reaction associated with mercurial diuresis to be due to digitalis mobilized from the edema fluid. The classical signs of disturbances in cardiac conduction, gastrointestinal and visual disturbances are well known. Barker¹² showed that in cases with associated renal damage, diuresis may produce concentration of nitrogenous waste products with resulting uremia.

Symptoms caused by the mercury portion of the molecule may be those of gastrointestinal or renal irritation. Anuria occasionally results. Various cutaneous eruptions have been noted. The cardiotoxic effects of mercurial diuretics probably should be included in this group, although experimentally ventricular fibrillation or ventricular asystole may occur depending on the type of mercurial used suggesting a specification related to chemical structure.¹³ Electrocardiographic tracing demonstrating ventricular fibrillation as the cause of death in two patients who had received esidrone intravenously have been presented by Volini, Levitt and Martin.¹⁴

Reactions related to the organic structure of the mercurial compound include precipitation of gout and allergic manifestations. While many of the cases of sudden death resulting from intravenous injection of mercurial diuretics were considered to be "anaphylactoid," evidence for the allergic nature of reactions to mercurial diuretics has only occasionally been presented. Gottlieb¹⁵ reviewed allergic reactions to mercurial diuretics and reported the case of a patient who developed urticaria seven hours after the intravenous injection of mercupurin and in whom a patch-abrasion test was markedly positive. Urticaria has been noted by other observers.¹⁶ Burrows and Stokes¹⁷ reported nine cases of erythematous eruptions following neptal with transient positive patch tests. Delayed asthmatic reactions¹⁸ and pulmonary edema¹⁹ have been noted. It has been observed that some patients develop reactions following a particular mercurial but may take another with impunity.²⁰ Fox, Gold and Leon²¹ observed a patient with severe reactions following mercupurin and mild reactions following salyrgan, neptal and mercurin suppository.

The following two cases are felt to be worthy of presentation because (1) no previous fatality due to mercurhydrin has been reported, in fact severe reactions appear to be exceedingly uncommon, (2) only one death has been previously reported following intramuscular injection of a mercurial diuretic. The cause of death in that case was due to renal failure, while in our case the mechanism was apparently different, and (3) observations were made concerning the mechanism of the adverse reaction.

CASE REPORTS

Case 1. A 50 year old white laborer was admitted to the hospital with hypertensive cardiovascular disease because of pulmonary and peripheral edema. Admission blood pressure was 170/100 mm. Hg.

Laboratory examinations showed a persistent low grade pyuria. On the sixth hospital day 20 to 25 casts per low power field were observed. Urinary specific gravity on admission was 1.020. There was no urinary albumin or glucose. On the fifth hospital day the blood level of non-protein nitrogen was 70 mg. per 100 c.c., urea nitrogen 44 mg. and creatinine 2.9 mg. The urea clearance test showed 48 per cent of average normal clearance, and the Fishberg concentration test showed concentration to 1.022. Serum albumin was 4.6 and globulin 1.7 grams per 100 c.c.

The electrocardiogram was normal.

Course and Treatment: The patient was placed on a 1,500 calorie low sodium diet and was given mercurhydrin 2 c.c. intramuscularly daily. A steady weight loss of 20 pounds (9 kg.) in 16 days took place. There was a low grade fever, temperature varying between 99° F. and 100° F. and rising to 101° F. on the eighth hospital day. During the next two days the temperature was normal in the morning and rose to 101° F. and 102° F., respectively, following the morning injection of mercurhydrin, and the patient complained of retrobulbar pain, weakness and dizziness following injection. On the tenth hospital day he developed a diffuse erythema of his back and a blotchy erythema of the chest and abdomen. White blood cell count at that time was 5,800 per cu. mm. with 70 per cent neutrophils, 24 per cent lymphocytes, 5 per cent monocytes and 1 per cent basophiles. Urinalysis showed 12 to 15 white cells and no albumin or sugar. At this point the mercurhydrin injections were discontinued. The temperature promptly returned to normal and did not go above 99.6° F. until the day of death. There was a continued decrease in weight of 5 pounds (2.7 kg.). On the eighteenth hospital day a weight gain of 3 pounds (1.4 kg.) occurred, and the patient developed edema of the ankles and râles in both lung bases. At 3:00 p.m. 2 c.c. of mercurhydrin were given intramuscularly. Within 30 minutes the patient complained of severe pain in his eyes and head and in the lumbar region. There was associated tingling all over his body, shortness of breath, nausea, and vomiting of a large amount of blood-tinged liquid. Aminophyllin, 0.25 gm., was given intravenously. This was followed by chills and cyanosis. The extremities became cold. Sodium phenobarbital, 0.3 gm., was given intramuscularly. Oxygen was administered by mask. At 5:00 p.m. the patient complained of a constricting pain across the chest laterally and subternally. The blood pressure was 94/52 with an irregular pulse of 132. Because of a presumptive diagnosis of coronary occlusion, 15 mg. of morphine sulfate were given intravenously with alleviation of symptoms. At 7:00 p.m. the patient complained of numbness of the right foot, and the foot was pale and cold although pulsations of the dorsalis pedis and posterior tibial arteries were present. At 7:20 p.m. the color returned to the foot and it became warm. Dyspnea recurred at 7:30 p.m. and 0.25 gm. of aminophyllin was again given intravenously. At 8:00 p.m. the patient suddenly went into profound shock, and in spite of adrenalin administered intracardially, he died at 8:15 p.m.

At necropsy the body was obese weighing about 260 pounds (118 kg.) and was about 5' 11" (180 cm.) long. There was pitting edema of the legs and cyanosis. Minimal bilateral hydrothorax and hydropericardium, and chronic passive congestion of the lungs, liver, spleen, kidneys and gastrointestinal tract were noted. The heart weighed 550 gm. and the left ventricular wall was 20 mm. thick. The coronary arteries were patent. The kidneys were not enlarged. The capsule stripped with ease leaving a smooth surface.

Pertinent microscopic findings were present in the kidneys, stomach and brain.

The kidneys (figure 1) demonstrated a striking pallor of the cortex contrasting sharply with the extreme vascularity of the medullary portion. The majority of glomeruli were pale and bloodless and were swollen so that Bowman's capsular space was very narrow. There was extensive necrosis of the proximal convoluted tubules. Many tubules were filled with desquamated necrotic epithelial cells and in other

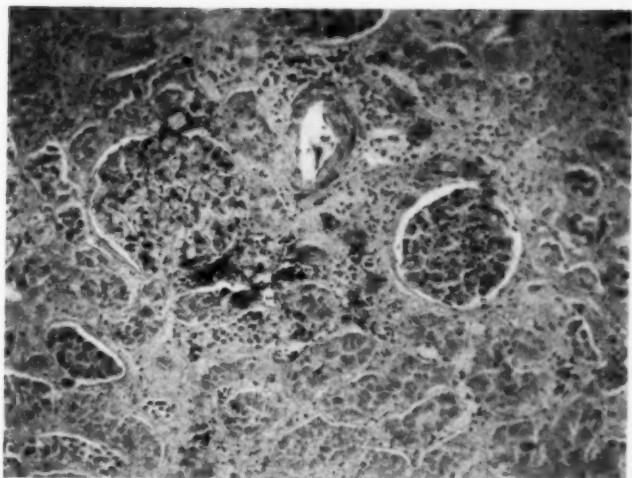


FIG. 1a. Kidney ($\times 100$), H. and E. stain. Note the swollen glomeruli and the extensive degeneration of the proximal convoluted tubules.

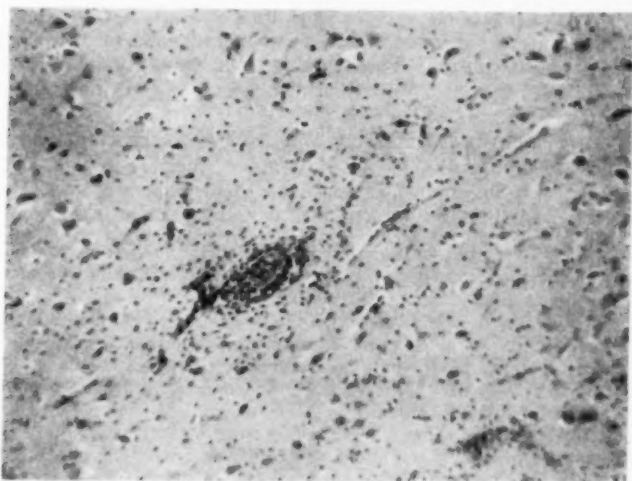


FIG. 1b. Brain ($\times 100$), H. and E. stain. Note the perivascular cuffing.

tubules the epithelial cells were swollen, almost completely filling the lumen. Some necrosis was present also in the distal convoluted tubules. The striking involvement, however, occurred in the proximal tubules. The collecting tubules showed well-preserved epithelium. Except for small subcapsular scars, no significant change was present in the interstitial tissue. There was slight hyaline thickening of the small arteries and an occasional arteriole showed marked hyaline thickening.

The brain (figure 2) showed well-developed perivascular infiltration of the blood vessels of the white matter. The cells were small lymphocytes with some monocytes and histiocytes. The vessel walls were unchanged. The architecture of the cortex was well preserved. Rare individual neurons showed acute swelling. There was no inflammation of the leptomeninges, and their blood vessels were normal.

The mucosa of the stomach showed extensive congestion with hemorrhage and superficial erosions.

An incidental finding was a nodular goiter.

COMMENT

It is felt that death in this case was due to the injection of mercurhydrin for the following reasons: (1) subjective symptoms were reported by the patient following each of the last four injections, (2) elevations in temperature were related to the injection of mercurhydrin, and (3) the reaction which terminated in death began within 30 minutes of the intramuscular administration of mercurhydrin.

Acute toxic nephrosis produced by mercurial diuretics has been reported previously. Schwab, Herrmann and Stone²² observed two cases of anuria following prolonged use of salyrgan in which postmortem examination revealed extensive tubular damage. Waife and Pratt⁴ found similar renal damage in a patient who died in anuria four days after an injection of mercupurin. No diuresis had followed the preceding injection in their case. In our case diuresis occurred with the preceding injection and the fatal reaction was much more severe, death occurring much too rapidly (within six hours) for the nephrosis to be the primary cause of death. This suggests the likelihood of a different mechanism, possibly an anaphylactoid reaction. The significance of the brain changes is not clear.

The fatal reaction was foreshadowed by subjective complaints and by temperature elevations following the three previous injections. These had been noted and correctly interpreted as reactions to mercurhydrin by the patient's physician, but the full danger of continued administration was not appreciated.

Case 2. A 56 year old white laborer was admitted to the hospital because of pulmonary and peripheral edema due to aortic insufficiency following rheumatic fever. There was no personal or familial history of allergy.

The admission blood count showed 7,000 white cells per cu. mm. and 14 gm. of hemoglobin per 100 c.c. The differential count was 65 per cent neutrophils, 27 per cent lymphocytes, 3 per cent monocytes and 5 per cent eosinophiles. Urinalysis showed a specific gravity of 1.023, no albumin or sugar, 0 to 2 casts per low power field and an occasional white blood cell per high power field.

The electrocardiogram showed negative T-waves in all chest leads.

Course and Treatment: The patient was placed on a low sodium diet, was digitized with digitoxin and was given 2 c.c. mercurhydrin intramuscularly daily. On the tenth hospital day shortly after his tenth injection of mercurhydrin he complained of weakness and mild dizziness, and his temperature rose from 97.0° F. at 8:00 a.m. to 101.4° F. at 8:00 p.m. On the following day, again after mercurhydrin, his temperature rose from 97.0° F. in the morning to 101.0° F. in the evening, and early in the evening he complained of extreme fatigue. Mercurhydrin was withheld until the fourteenth hospital day, when 2 c.c. were given intramuscularly at 8:00 a.m. In less than an hour (exact interval not known) he complained of nausea and headache. This was followed by vomiting and coughing. At noon he had chills, and slight

cyanosis was noted. He became very restless and confused. By 4:00 p.m. his temperature had risen to 104.6° F. (rectal) and his pulse rate was 116. By 5:15 p.m. he was totally disoriented. There was a marked flush. The pulse rate was 140. The chest was free of râles. The non-protein nitrogen level at this time was 44 mg. per 100 c.c. At 6:00 p.m. he was given an intravenous infusion of 1000 c.c. of 5 per cent glucose in distilled water. At 9:00 p.m. he was incontinent of urine and had generalized twitchings and clonic contractions of flexors and extensors of all extremities. He became comatose, and death was felt to be imminent. He was given 0.5 gm. of sodium amytal intravenously and 1 gm. calcium gluconate in 1,000 c.c. of 5 per cent glucose in distilled water at 9:00 p.m. He continued to cough up large amounts of mucus.

On the following day he was still incontinent and drowsy but could be roused. One thousand c.c. of 5 per cent glucose in distilled water were again given intravenously; and 0.12 gm. of sodium phenobarbital was given intramuscularly. His condition remained unchanged until late in the third day when he recovered enough to be up and about, but he did not feel well for another two or three days.

Mercuhydrin was suspected as a possible cause of this reaction and was withheld for 11 days. Then a trial dose of 0.25 c.c. was given intramuscularly. Within about a half hour the patient complained of headache, vomiting and aching in all joints. He was again somewhat confused. His temperature rose to 100.2° F. by 2:00 p.m., reaching 101° F. at 4:00 p.m. and returned to 98.6° F. by 6:00 p.m. Except for headache the patient felt well on the following day.

He was then given mercupurin .05 c.c. intramuscularly. This was doubled daily until a 2 c.c. dose was reached. No adverse reaction took place. Aminophyllin, 75 c.c. (containing the equivalent of the theophylline contained in 0.25 c.c. of mercurhydrin) had no effect. Because of the absence of reaction to mercupurin he was again tested with .05 c.c. mercurhydrin intramuscularly. Within 90 minutes he began having generalized aching and chills. He was moderately flushed and was sweating. Blood pressure was 160/60 mm. Hg. He vomited copiously during the next several hours and complained of moderate headache. Unexpectedly the temperature fell to 97° F. (oral) one-half hour after the injection and to 96° F. within two and one-half hours of the injection, remaining at 96° F. for about six hours and then rising to 98.6° F. The headache persisted on the following day, and it was several days before he felt well.

An attempt was made to confirm an allergic basis for these reactions by several tests. These tests, however, were not performed until three months after the last reaction occurred. Direct intradermal tests were applied using (1) the serum of a patient on maintenance doses of mercurhydrin, (2) mercurhydrin diluted 1:1,000 in normal serum, and (3) mercurhydrin diluted 1:1,000 in saline. Normal serum and a serum-mercupurin mixture were used as controls. Inconsistent reactions occurred in repeated tests. Passive transfer tests were made using (1) the direct Prausnitz-Küster method (skin sites of non-sensitive individuals prepared with the patient's serum and injected 48 hours later with the test materials used in the skin tests), (2) the reverse Prausnitz-Küster method (sites prepared with test materials injected in 48 hours with the patient's serum), and (3) mercurhydrin given intramuscularly to a test subject 24 hours after receiving intradermal injections of the patient's serum. These passive transfer tests gave no reactions.

COMMENT

The reactions in this patient are thought to be allergic for the following reasons: (1) reactions did not occur following the initial injections of mercurhydrin, (2) a severe reaction followed the injection of 0.05 c.c. of mercurhydrin, a neg-

ligible amount from the standpoint of toxicity, and (3) unfavorable reactions did not occur following the injection of 2 c.c. of mercupurin. The failure to demonstrate allergens is usual in drug allergies but may have been due to delay in testing, as positive reactions observed by Gelfand became negative several months after cessation of therapy.²⁴

The reaction can be explained on the basis of a vascular hypersensitivity. The symptoms suggested transitory diffuse brain involvement with disturbances in temperature regulation suggesting involvement of the hypothalamus.

The severe reaction was foreshadowed by temperature elevations and by subjective complaints following the two preceding injections of mercurhydrin.

CONCLUSIONS

1. Using the intramuscular route for administering mercurial diuretics does not safeguard against unfavorable reactions.
2. Mild reactions should be regarded as danger signals, and therapy should be reevaluated. If a mercurial diuretic is indispensable, a small dose of a different compound may be given and the patient observed for unfavorable reactions before therapeutic doses are used.
3. The routine use of daily parenteral injections of 2 c.c. of a mercurial diuretic is to be condemned. The aim should be to give small doses frequently. In this regard oral administration of mercurial diuretics, allowing constant minimal dosage, should be considered whenever possible.
4. The occasional occurrence of an unfavorable response to mercurial diuretics should not restrain physicians from their use. Mercurial diuretics remain among the most valuable drugs available for the treatment of congestive failure.

We thank Dr. Harry Goldblatt who reviewed the microscopic sections of the kidneys.

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MONOCYTIC LEUKEMIA, AN UNCOMMON CAUSE OF RENAL FAILURE *

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and IRVINE H. PAGE, M.D., F.A.C.P., *Cleveland, Ohio*

MOST causes of renal failure are easily recognized. However, the record of the patient reported here presents an example of death due to renal insufficiency, the mechanism of which was not clear until autopsy had been performed. The kidneys were found to be almost completely replaced by leukemic tissue. Such infiltration of kidneys to a degree great enough to cause uremia is uncommon.

CASE REPORT

A 50 year old Jewess was admitted to the Research Division of Cleveland Clinic Hospital because of progressive anasarca and weakness of short duration. She had been examined as an out-patient in the Clinic three years previously, when her arterial blood pressure was found to be 155/105 mm. Hg; urinalysis normal; blood urea 30 mg. per 100 c.c.; blood hemoglobin 13 gm. per 100 c.c., and the white blood count 8,300 per cu. mm. Except for obesity and associated dyspnea she remained well until the onset of her final illness.

Two weeks before the last admission she consulted her physician because of generalized weakness, pain in the calves of her legs and mild hot flashes. Her complaints were thought to be due to menopause and she was treated with intramuscular

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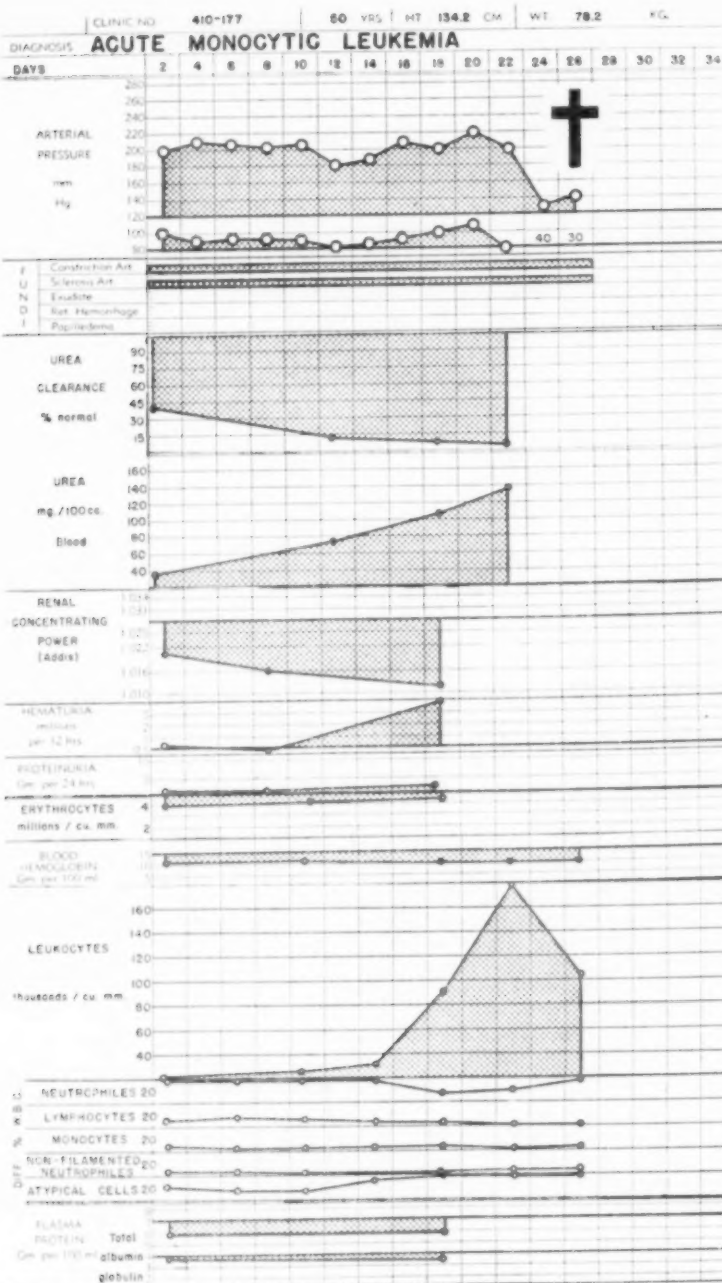


CHART 1.

theelin. Within 48 hours anasarca developed. Seven days later she again received an injection of theelin in oil. Edema promptly became more severe and she was referred to Cleveland Clinic Hospital.

The patient was 61 inches in height and weighed 173.5 pounds. The conjunctivae, face and extremities were edematous. Temperature was 99° F.; pulse rate 80 and blood pressure 210/100 mm. Hg. The optic discs and retinæ were normal. The retinal arterioles showed grade 2 narrowing. The red blood cell count was 4,370,000 per cu. mm.; blood hemoglobin 10.5 gm. per 100 c.c.; white blood count 15,700 per cu. mm.; urea clearance 45 per cent of average normal and blood urea 39 mg. per

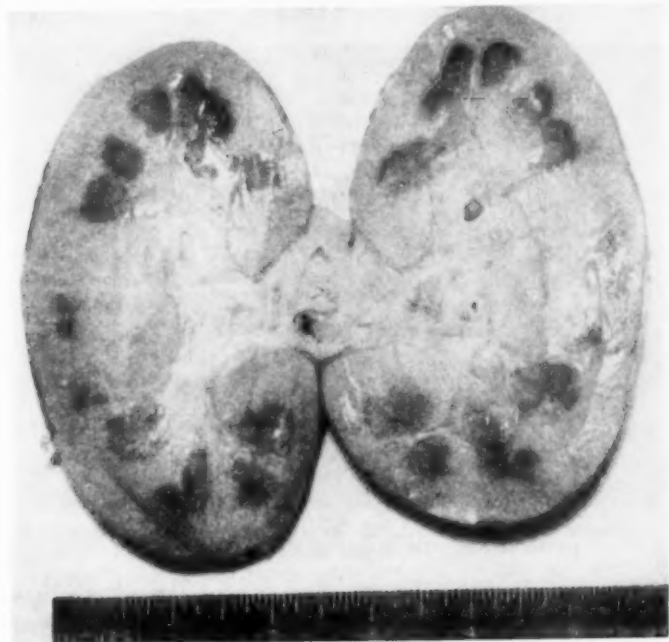


FIG. 1. The cut surfaces of the left kidney (328 gm.) show thickening of the capsule, the bulging parenchymal tissue and the alteration of normal markings. The cortex was 1.3 cm. in thickness.

100 c.c. The maximal ability to concentrate urine, as measured by the Addis test, was represented by a specific gravity of 1.020. There was 1.0 gm. of proteinuria per 24 hours. The Addis count of the urinary sediment showed 500,000 casts and a normal number of red and white cells. Intravenous and retrograde pyelograms were normal. Urine cultures were repeatedly negative. The electrocardiogram was within normal limits. Teleroentgenogram showed a cardiac shadow, the transverse diameter of which deviated plus 5 per cent from the predicted normal (Ungerleider and Clark¹).

The course of her illness is summarized in chart 1. The outstanding features were rapid renal failure and mounting leukocytosis. No clear explanation of either could be established. Significant anemia, lymphadenopathy, splenic or hepatic enlargement were not found. Gross hematuria due to acute hemorrhagic cystitis occurred once following cystoscopy. Urine specimens taken at this time were sterile.

The total white blood cell count gradually rose from the admission level of 15,700 per cu. mm. to 33,150, 10 days before death. Five days later it was 93,000 and after another 48 hours 192,000 per cu. mm. of blood. Of these, 55 per cent were atypical mononuclear cells, half of which gave a positive peroxidase reaction. There were 36 per cent neutrophils, 3.6 per cent nonfilamented neutrophils, 2.5 per cent lymphocytes, 2 per cent monocytes and 1 per cent myelocytes. Aspiration and surgical biopsies of the sternal marrow taken ante mortem were examined by Dr. L. W. Diggs.* Both showed moderately increased cellularity with normal myeloid and erythroid distribution. There was slight increase of reticuloendothelial and large mononuclear cells; however, none was considered pathognomonic of neoplastic disease. Dr. Diggs

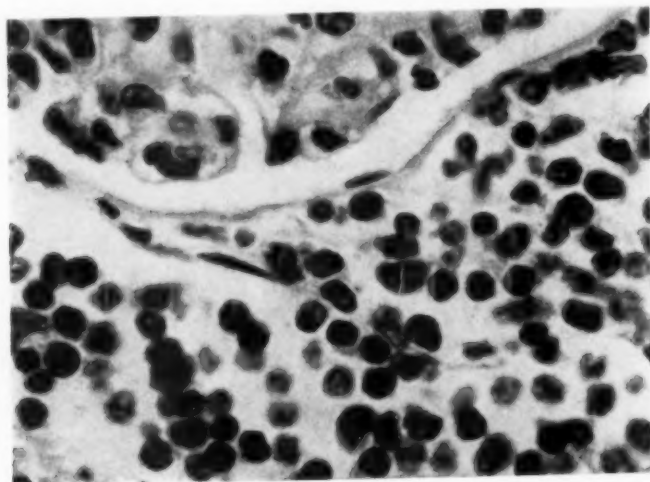


FIG. 2. Infiltration of glomeruli, tubular and interstitial tissue with monocytes is illustrated by this section. The tubular tissue is hardly discernible.

felt that the absence of pathological cells of the type noted in peripheral blood was against a diagnosis of leukemia. He suggested that there was probably a reticulum cell sarcoma with a leukemoid reaction of the bone marrow.

She became anuric three days before death and died on the twenty-fifth hospital day.

Pathological Report: Only the kidneys, spleen, sections of the liver and pancreas could be obtained for postmortem study.

The kidneys were twice normal size, the right weighing 308 gm. and the left 328 gm. (normal 115-155 gm.). There was moderate thickening of the capsules which stripped with increased difficulty. The external surfaces were pale, yellowish-brown and granular. The cut surfaces bulged and the cortices, which appeared swollen, measured as much as 1.3 cm. in thickness (figure 1). The pyramids were indistinctly demarcated from the cortices and were deep yellowish-brown color. Microscopic examination (figure 2) showed that the entire kidney was diffusely and heavily infiltrated by monocytic cells. The tubules were dilated and lined by degenerated epithelium.

* Clinical Pathologist, Cleveland Clinic Foundation.

The spleen weighed 430 gm. and was covered by a thickened tense capsule. On the cut surface the lymphoid follicles were prominent as pale gray circular areas measuring up to 1 mm. in diameter. Microscopically there was diffuse infiltration of monocytes.

The mononuclear cells throughout the tissues examined contained oval or indented nuclei filled with irregularly distributed chromatin. The nuclei were surrounded by a scanty amount of faintly basophilic cytoplasm. No definite grooving could be seen. The peroxidase reaction showed that numerous cells contained granules, and staining by the Kingsley method demonstrated many of the abnormal cells to be mononuclear resembling immature myelocytes.

The pathological diagnosis was monocytic leukemia (Naegeli type).²

COMMENT

Extensive studies conducted during the first two weeks of hospitalization demonstrated no cause for rapid renal failure or anasarca. There was no evidence of congestive heart failure, acute nephritis, hypoproteinemia (plasma albumin was 3.26 gm. per 100 c.c.) or appreciable anemia. Excessive retention of sodium and water was the only explanation that seemed tenable. This could have come about if there was glomerulo-tubular imbalance with a disproportionately great reabsorption of filtrate. That this might have existed was suggested by the Addis test done 14 days before death. The 12 hour volume was only 285 c.c. (normal 150 to 400 c.c.) and the maximum specific gravity was 1.016 while the urea clearance was depressed to 15 per cent of normal. Further, the cast count of the urinary sediment was 1.5 million per 12 hours with but 0.7 gm. of proteinuria per 24 hours. This might indicate sluggish flow of urine through tubules. Such glomerulo-tubular imbalance is seen in patients with toxemia of pregnancy and acute nephritis. It has been suggested that increased interstitial pressure within the kidneys might reduce glomerular filtration pressure while tubular reabsorption is comparatively unaffected.

The excessive leukocytosis which appeared terminally suggested some type of leukemia; however, neither the peripheral blood, lymph nodes nor bone marrow were typical of any given type. It was assumed that the rapidly rising white cell count represented a leukemoid response to a neoplastic process which probably was infiltrating the kidneys to cause increased intracapsular pressure which effectively reduced filtration pressure and resulted in glomerulo-tubular imbalance, and eventually renal failure and death. Postmortem examination demonstrated extensive infiltration of both kidneys by monocytes.

The liver and spleen were similarly infiltrated. The spleen weighed 430 gm. as compared with the normal values of 120 to 180 gm. It is probable that this enlargement was masked by obesity and ascites during life. Had the extreme leukocytosis occurred earlier the possibility of monocytic infiltration of the kidneys might have been considered, at which time a liver biopsy would have been helpful.

SUMMARY

A 50 year old woman developed anasarca and died of rapid renal failure of somewhat obscure origin. The explanation proposed for the generalized edema was sodium and fluid retention due to glomerulo-tubular imbalance. Extreme terminal leukocytosis suggested that infiltration of the kidneys by monocytes

might have increased intracapsular pressure enough to produce this syndrome. Examination of the bone marrow and peripheral blood did not allow for exact diagnosis but it seemed probable that a reticulum cell sarcoma was infiltrating the kidneys and inducing a leukemoid reaction of the bone marrow. At post-mortem examination the kidneys, liver and spleen were found infiltrated with the cells of acute monocytic leukemia. The diagnosis could have been made ante-mortem had peritoneoscopy and biopsy of the liver or spleen been done.

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SPLANCHNICECTOMY FOR HYPERTENSION IN LUPUS ERYTHEMATOSUS AND PERIARTERITIS NODOSA *

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ONE of the most important advances in the treatment of hypertension is the bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy.^{4, 5, 9} However, the articles written on the subject have been concerned entirely with patients who have had essential or malignant hypertension. No reports have been presented in which this operation was performed for hypertension secondary to a generalized disease. This report is of one case of periarteritis nodosa, in which the outstanding lesion is arterial necrosis and one of disseminated lupus erythematosus in which the striking finding is widespread fibrinoid degeneration of the collagenous tissue, necrosis of the arterial walls, proliferative endarteritis and in some areas thrombosis of the arteries. No attempt will be made to discuss either the diseases or the operative technic since there are numerous articles¹⁻¹⁰ in which they are covered in detail.

CASE REPORTS

Case 1. A 36 year old white male was admitted to the University Hospital on November 5, 1940, complaining of pain in the arms and legs of five months' duration.

Present Illness: Nine years prior to admission this patient had had pain in the muscles of the arms and legs which persisted for three months and disappeared completely after extraction of his teeth. He was in good health until one year before admission when he began to lose weight without apparent change in his appetite. He had lost 24 pounds in one year. Five months prior to admission he developed severe, stabbing pains in the legs which soon involved the arms and neck. The pain seemed to be in the joints and muscles, was aggravated by cold and by exercise and all of his joints were painful on motion. At the time of the onset of the pain he had severe

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mid-epigastric pain with nausea and vomiting for 10 days which disappeared spontaneously and did not recur. The pain in the muscles and joints gradually became more severe and at the time of admission was relieved only by opiates. During the previous year he had had occasional nosebleeds and for a period of one month, three months before admission, he noted morning eyelid puffiness and ankle edema which cleared up spontaneously and did not recur. Two weeks prior to his admission to the hospital he had a cerebral vascular accident which resolved without residual signs. At that time his systolic blood pressure was said to be 220 mm. of mercury.

Physical Examination: Blood pressure 200/120 (R) and 180/115 (L). The patient was a chronically ill, poorly nourished white man complaining of severe pain in the legs and arms. Examination of the eyes revealed a group IV neuroretinitis (Keith-Wagner-Craig) with hemorrhages, exudate and papilledema. The heart was not enlarged, but the second aortic sound was loud and there was a soft apical systolic murmur. The liver was palpable 1 cm. below the right costal margin. Some observers felt that nodules could be palpated along the brachial arteries. The remainder of the examination including a complete neurological survey was essentially negative.

Laboratory Findings: Red blood cell count 5,800,000 per cu. mm. Hemoglobin 15.6 gm. (Sahli). White blood cell count 20,650 per cu. mm. with a differential count of 78 per cent polymorphonuclears, 2 per cent eosinophiles, 14 per cent lymphocytes and 6 per cent monocytes. Urinalysis revealed a trace to 2 plus albumin, an occasional red and white blood cell and occasional granular and hyaline casts. Blood non-protein nitrogen was 32.5 mg. per cent. The urea clearance test showed 159 per cent excretion in one hour and 116 per cent in two hours. Blood Kahn test negative. The electrocardiogram was suggestive of right ventricular hypertrophy and an orthodiagram was normal. Intravenous pyelograms were negative. A biopsy of the gastrocnemius muscle (November 11, 1940) was reported by Dr. C. V. Weller as follows: "The skin and subcutaneous tissues, including nerves, show no evidence of arterial disease. There are no infiltrations around the smaller vessels. In the voluntary muscle the arterioles show some sclerosis and there is one small compact lymphocytic infiltration around several arterioles. This is unlike angiomysitis and periarteritis nodosa in that the arterioles in the infiltration show no necrosis or other alteration in their walls. We believe that this infiltration must have some other explanation. It does not suggest trichinosis since there are no eosinophiles."

Course in the Hospital: The patient was seen in consultation by a neurologist who made a diagnosis of a subsiding subarachnoid hemorrhage and by an ophthalmological consultant who concurred in the diagnosis of grade IV neuroretinitis. His pre-operative course was marked by severe pain which required opiates for relief. The blood pressure varied from 180/120 to 240/140. On November 15, 1940, a splanchnicectomy was performed and the pathological report by Dr. C. V. Weller on the tissue removed at operation was as follows: "Right splanchnic nerve and ganglion showing operative trauma. Voluntary muscle shows operative trauma. No inflammatory infiltrations. Intercoastal artery not thickened. Left splanchnic nerve and ganglion show operative trauma. This contains adipose tissue and fascia with medium sized arteries. One of these arteries shows necrosis of its wall with hyaline changes, some yielding of the wall and a subacute periarteritis with many new formed blood vessels. These changes are compatible with periarteritis nodosa."

For three days following operation the patient had hypotension and was free from pain. On the fourth post-operative day there was a progressive rise in blood pressure and return of pain. He was discharged on December 5, 1940, and it was felt that his prognosis was extremely poor.

Follow-up: December 14, 1940, a letter from the patient's physician reports severe muscle pain, visual field defects, urinary infection and a blood pressure of 110/75 to 160/110.

On December 6, 1941, a letter from the patient's wife reports that he is completely well. His blood pressure is said to be normal and the pains have completely disappeared. He is leading a normal, active life.

November 16, 1946: The following are excerpts from a letter received in answer to a letter requesting the patient to return for reexamination: "As I am very busy right now getting out fall orders and answering correspondence, I will be pleased to give information herein. I was checked for blood pressure a few weeks ago by Dr. L., who said 'your pressure is perfect.' Got myself some glasses a few years ago and my sight has improved very much during the past several years. As a hobby I have been grinding lenses for binoculars."

A subsequent letter from the family physician states that the patient's blood pressure was 132/80 in October 1947.

Case 2. A 42 year old white married female was first admitted to the University Hospital on March 14, 1947.

Five years prior to this admission she developed a rash over the nose, cheeks and forehead which was diagnosed as lupus erythematosus and for which she received 20 injections of a gold compound, 20 of bismuth and a course of a sulfonamide. This therapy resulted in disappearance of the rash and only atrophic scars remained. She had a low grade fever during this episode; however, the fever disappeared and the patient was well until May 1945, when the eruption reappeared. It spread to involve the "V of the neck," upper back and tips of the fingers and she developed a rheumatoid-like arthritis of the left hand. She was treated with bed rest and liver extract, but did not improve.

Physical Examination: Temperature 101° F. Pulse 114. Respirations 32. Blood pressure 150/100 mm. Hg. The patient was pale and appeared chronically ill. There was a papulo-squamous rash over the nose, cheeks and forehead in which there were areas of atrophic scarring and residual pigmentation. There was minimal generalized alopecia as well as several areas of alopecia associated with atrophic scars. The fingertips of the left hand were erythematous and showed telangiectasia. Examination of the eyegrounds revealed narrowing and tortuosity of the arterioles, hemorrhages and exudate and papilledema with secondary optic atrophy. Visualization of the fundi was difficult because of a congenital horizontal nystagmus. The remainder of the physical examination was not remarkable.

Laboratory Findings: Red blood cell count was 4,100,000 per cu. mm. Hemoglobin 13.0 gm. (Sahli). White blood cell count was 4,100 per cu. mm. with the differential count showing 68 per cent polymorphonuclears, 25 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophiles. Urinalysis was normal except for a 1 plus albumin, specific gravity of 1.014 and 3 to 5 red blood cells and an occasional white blood cell per high power field. The urea clearance test showed 33 per cent excretion in one hour and 39 per cent in two hours. The blood urea nitrogen was 14 mg. per cent. A bromsulfalein test showed 5 per cent retention in 45 minutes. The electrocardiogram and an orthodiagram were normal. Blood Kahn test negative.

Course in the Hospital: She remained in the hospital for 14 days. Her temperature varied from 100 to 101° F. during the first 11 days, but was less than 100° F. during the last three days. She was treated first with Lugol's solution and later with oridine. She complained of frequent, severe, occipital headache, weakness and, at times, malaise. She was given two transfusions of 250 c.c. of whole blood and was discharged March 28, 1946, somewhat improved.

Following discharge she gradually became worse and was readmitted August 15, 1946. There had been a progressive rise in blood pressure with severe occipital and generalized headaches, periods of mental confusion and almost complete blindness. She also complained of recurrent nausea and vomiting and mild exertional dyspnea.

Physical Examination (Second Admission): Temperature 97.6° F. Pulse 80. Respirations 22. Blood pressure 216/126 mm. Hg. The patient was well developed

and fairly well nourished but appeared chronically ill. She had transitory periods of mental confusion, difficulty in memory and could see only the outlines of objects. Examination of the optic fundi revealed a more severe hypertensive retinitis than was present on the first admission. There was papilledema with secondary optic atrophy, marked spasm of the arterioles and extensive hemorrhage and exudates. There were many depressed, atrophic, depigmented scars over the face, scalp and upper chest, but no evidence of active lesions. The skin of the tips of the fingers was thin and atrophic with marked telangiectasia. Examination of the heart revealed slight enlargement to the left, a loud second aortic sound and a soft systolic murmur along the left sternal border. The remainder of the physical examination was not remarkable.

Laboratory Findings: Hemoglobin 11.5 gm. (Sahli). Red blood cell count 4,100,000 per cu. mm. White blood cell count 6,200 per cu. mm. with a differential count of 68 per cent polymorphonuclears, 2 per cent eosinophiles, 26 per cent lymphocytes and 4 per cent monocytes. Repeated urinalysis showed a 1 to 3 plus albumin, 0 to 4 red blood cells, many white blood cells, an occasional granular cast per high power field and a specific gravity from 1.005 to 1.021. The blood non-protein nitrogen was 38.7 mg. per cent. The urea clearance test showed 45 per cent excretion in one hour and 36 per cent in two hours. The electrocardiogram was normal. An orthodiagram showed slight cardiac enlargement to the left.

Course in the Hospital: The patient complained of severe headaches which were not relieved by nitroglycerin or acetosalicylic acid-phenacetin-caffeine tablets. She was seen by a medical consultant who did studies with tetra-ethyl-ammonium-chloride and found no drop in blood pressure after injection of the drug. On August 26, 1946, a splanchicectomy was performed. She reacted slowly and the post-operative course was stormy. The patient had periods of apnea with cyanosis and required intra-nasal oxygen therapy, as well as intravenous plasma and glucose. She developed a post-operative urinary infection which responded to sulamyd. She gradually recovered from the operation. Eighteen days after the operation the headaches had disappeared and her vision seemed better, but there was no change in the fundusoscopic findings.

She was encouraged to get out of bed, but she had difficulty in doing so because of syncope. It was noted that she had a postural hypotension, her blood pressure falling from a recumbent level of 172/110 to 130/90 after standing for one minute. With an abdominal corset applied and her legs wrapped with elastic bandages her respective blood pressure readings became 170/110 and 146/90, and she was able to sit up, although she required repeated encouragement. She was discharged September 22, 1946, on parenteral vitamins and advised to get up and about as much as possible.

Follow-up: She continued to do well for a period of two months, but soon had a return of her symptoms of headache, anorexia and insomnia. Her blood pressure gradually rose to 220/140, fresh retinal hemorrhages appeared and she died in uremia approximately six months after discharge from the hospital.

COMMENT

The vast number, as well as the great differences in pharmacologic principles of the recommended treatments for periarteritis nodosa and disseminated lupus erythematosus are sufficient proof of the inefficiency of all therapy in spite of temporary improvement in a few patients from a wide variety of therapeutic procedures. Thus, it seems obvious that any procedure which offers hope of relieving one of the manifestations of the diseases is worth a trial. We realize that this procedure is not applicable to all cases and that it may be nothing more than another addition to the long list of ineffective forms of treatment. The patient with periarteritis nodosa has apparently made a complete recovery and has remained

in good health for six years after operation. This is a surprising result and the explanation is not apparent, unless one assumes that the etiological factor causing the periarteritis nodosa was dissipated. The patient with disseminated lupus erythematosus had temporary benefit, both symptomatically and objectively, but the eventual outcome was not altered.

The post-operative course of the first patient throws some light on the possible mechanism of pain in periarteritis nodosa. For three days after operation his systolic blood pressure did not rise above 100 mm. of mercury (average 94/70) and he was free from pain during this time. On the fourth postoperative day there was a rise in the blood pressure to 136/72 mm. Hg and a coincident return of pain. It seems likely that the systolic blood pressure, by producing sudden thrusts and stretching the walls of the necrotic arteries is an important factor in the production of pain in diseases associated with arterial necrosis.

On the basis of the results obtained in these two patients we believe that splanchnicectomy is a procedure to be seriously considered in patients with disseminated vascular diseases if hypertension is producing symptoms.

SUMMARY AND CONCLUSIONS

A patient with periarteritis nodosa and one with disseminated lupus erythematosus were subjected to splanchnicectomy because of hypertension. The follow-up shows an excellent result in the former for six years after treatment. In the latter there was improvement for two months, but no change in the usual outcome of the disease, the patient dying in uremia six months after discharge from the hospital. The surgical treatment of hypertension which occurs as a part of a generalized vascular disease is worthy of further trial and study. A possible explanation regarding the mechanism of pain in periarteritis nodosa is presented.

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METASTATIC ADENOCARCINOMA OF THE THYROID WITH ELEVATED BASAL METABOLISM: RADIOIODINE STUDIES *

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INCREASING interest has been shown in the use of radioiodine as a tool for the clinical investigation and therapy of various thyroid maladies. This has followed upon the availability of large amounts of the isotope prepared in the uranium pile. A number of cases have been reported in which tumors of the thyroid have been studied or treated by radioiodine,¹⁻¹⁰ and the literature has been recently reviewed by Rawson and McArthur.¹¹ Marinelli et al.¹⁰ have stated that, on the basis of their radioautographic study of various histopathologic types of carcinomas of the thyroid, together with an estimation of the relative frequency of the various types, approximately 15 per cent of thyroid cancers may be expected to accumulate radioactive iodine in some degree. Consequently, it was felt that a study with radioiodine of the patient to be presented here, who had adenocarcinoma of the thyroid with known metastases in the liver, was warranted. The subject was unusual, in that he also exhibited evidence of hyperthyroidism, a condition rarely associated with malignant thyroid tumors.^{7, 12-21}

CASE REPORT

A white male, age 54, was admitted to the Neuropsychiatric Hospital of the V.A. center at Los Angeles on January 3, 1945 by transfer from St. Elizabeth's Hospital, Washington, D. C. where he had been under treatment for paresis. Estimated duration of the luetic infection was 10 years. On admission to Wadsworth General Hospital June 19, 1947 he presented symptoms of dysphagia and dysphonia which followed progressive enlargement of the neck, first observed in January, 1947. Another presenting sign was abdominal enlargement with attendant discomfort of one month's duration. An indefinite epigastric mass had been noted at St. Elizabeth's Hospital in December 1944. A weight loss of 30 lbs. had been sustained over the preceding year (1946).

The physical examination June, 1947, revealed a very thin, euphoric patient in no acute distress. His pupils were irregular and reacted slowly to light. There was a symmetrical, firm bilateral enlargement of the thyroid gland measuring approximately 8 by 8 by 5 cm. with the isthmus easily palpable. No bruit was heard. There was no apparent retro-sternal extension. The chest was clear to percussion and auscultation but the left diaphragm was apparently slightly elevated. The patient was not dyspneic. The heart was within the limits of normal. The abdomen was scaphoid with a firm smooth mass in the epigastrium which extended midway to the umbilicus and moved with respiration. The mass could be moved transversely and

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presented an edge which was firm and slightly tender. Neurological examination revealed absent knee jerks and ankle jerks with a diminished vibratory sense at the ankles. Proprioceptive sensation was limited and a positive Romberg was elicited.

Pertinent laboratory data at this time demonstrated secondary anemia, a normal white cell count, normal blood iodine and negative blood Kahn and Wassermann tests. Blood urea nitrogen was 14 mg. per cent and urea clearance 43 per cent; numerous urinalyses were normal; basal metabolic rate: + 29, + 30 and + 26; total blood protein was 8.4 gm. per cent with a 1.7 A/G ratio and the icterus index was 9. The serum cholesterol was low but the thymol turbidity test of hepatic function was normal. Prothrombin time ranged between 68 and 83 per cent of normal. Bleeding and coagulation times were normal. A gastric analysis done in July, 1947 revealed no free acid in fasting or histamine stimulated specimens.

Diagnostic roentgenography for tumor was negative for (a) the gastrointestinal tract in July 1947, (b) the thorax in June and December 1947 and (c) the pelvis in October 1947. Roentgenographic survey of the entire skeleton in April 1948 gave no evidence of malignancy.

Biopsy specimens of the thyroid gland on July 30, 1947 and again on August 25, 1947 were diagnosed: "Papillary adenocarcinoma of the thyroid with extension through the capsule." Punch biopsy of the liver was diagnosed "metastatic adenocarcinoma of the thyroid in liver with foci of necrotic tissue."

The patient remained comfortable during his hospital stay. He did not complain of pain but was, in fact, in an euphoric state due to the parietic changes. Except for occasional slight temperature elevations he remained afebrile and ambulant, though somewhat weak and slightly ataxic. He was given general supportive treatment, including transfusion, until October 2, 1947 when roentgen-ray treatments twice weekly to thyroid and liver were instituted while the patient was in temporary residence at the Neuropsychiatric Hospital. Over a period of two weeks 1500 r. was given to the thyroid and 600 r. to the liver. Thereafter the thyroid diminished slightly in size. The dysphonia and dysphagia diminished although the left vocal cord remained paralyzed. Despite a gradual increase in size of the liver he was relieved of his dyspnea. The weight loss continued from the level of 102 lbs. of August 1947 and it was obvious that the irradiation had had little effect. The patient was then retransferred to the General Medical and Surgical Hospital.

On October 16, 1947 an oral dose of 1.17 millicuries of radioactive iodine (I^{131}) was given and an immediate and continuing survey of radioactivity was carried out. Biopsy specimens as well as specimens of blood and urine were taken at intervals and examined in a manner indicated elsewhere.

On February 24, 1948, at which time his general condition showed little change from the previous status, the patient was given orally 12 millicuries of I^{131} obtained through the kind cooperation of Dr. George M. Lyon, Chief, Radioisotope Section, U. S. Veterans Administration, Washington, D. C. and further studies were conducted. Liver and thyroid biopsies were made on March 2, after three transfusions of 500 c.c. each of whole blood had been given because of a prothrombin time about 30 per cent of the normal.

Relevant laboratory results at this time were: March 1, icterus index 7; blood Wassermann test negative; March 3 and 11, urinary albumin 2+ with 15 to 20 red blood cells per high power field; March 3, coagulation time 7 minutes and March 5, blood protein total 6.1 gm. per cent with A/G ratio 1.5. The white blood count diminished from 5150 (March 11) to 4000 on April 1. On April 21 it was 5900 with red blood cells 3.2 million. Evidence of renal damage regularly persisted, including albuminuria, hematuria and appearance of hyaline casts.

The biopsy specimens from thyroid and liver one week following ingestion of the radioiodine showed no definite microscopic change from the previous biopsy.

The patient's clinical course was unmarked by any critical episode but the trend was persistently downward. His previously cheerful euphoric cooperation was replaced by apathy, weakness and cachexia. His course was terminated by death on April 23, 1948. Pathological observations were performed April 27, 1948 by Dr. Leo Kaplan and Dr. B. Fishkin, Pathologists, General Medical and Surgical Hospital, U. S. Veterans Administration Center, Los Angeles.

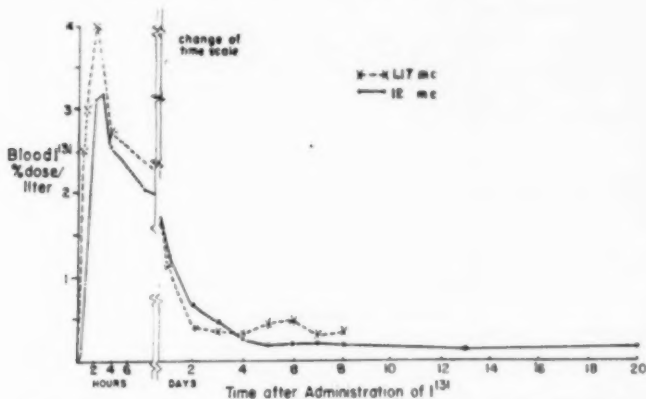


FIG. 1. Concentration of I^{131} in the blood. Data shown have been increased to correct for radioactive decay since the time of administration.

RADIOACTIVITY DATA

Methods: Radioiodine was administered orally in a small glass of water and rinsed down with another portion of water from the same glass. Measurements of relative radiation intensity over various portions of the body were made with a Victoreen portable Geiger counter model 263 with a thin steel beta-ray shield. In the measurements made after the first dose, a lead plate of approximately 0.5 in. thickness was held vertically between the thyroid and abdomen, touching the trunk about 3 cm. below the xiphoid process of the sternum. For the measurements of the body after the second dose, the lead plate was omitted, and a cylindrical lead shield around the Geiger counter tube was employed while trying to localize points of high radioactivity.

Aliquots of blood (50 to 100 microliters) and urine (1 to 100 microliters) were dried on metal planchettes and their radioactivity measured by a Technical Associates Geiger counter with a lead shielded beta-sensitive tube showing a background of approximately 20 counts per minute and an efficiency of about 6 per cent. A 20 per cent correction for self-absorption was made for blood samples. Self-absorption in urine was found to be negligible. Determinations were made in duplicate, and agreement between duplicates generally fell within ± 5 per cent. Except where specifically stated otherwise, radioactivity determinations made at various times after administration of radioiodine are rendered comparable by presenting the excretion and distribution data as they would have appeared if none of the isotope had been lost by radioactive decay.

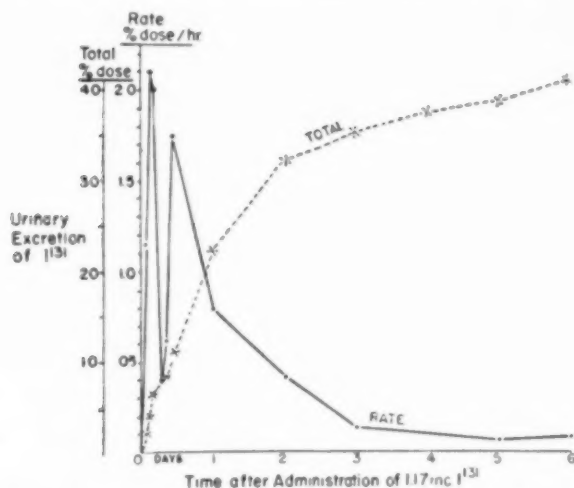


FIG. 2. Urinary excretion of I^{131} following oral administration of 1.17 mc. Data shown have been increased to correct for radioactive decay since the time of administration.

Results: 1.17 millicuries of I^{131} were given to the patient on October 16, 1947. The measurements of relative activity in various portions of the body were made as shown in table 1. At 24 hours, the activity in the lower abdominal region was slightly higher than the thyroid. Measurements attempted at 48 hours and later were unsatisfactory due to fluctuating sensitivity of the counter. The data obtained on blood and urine are shown in figures 1 and 2. The relatively low excretion in the urine of only about 35 per cent of the dose during the first three days is indicative of hyperthyroid activity or tumor uptake or both.¹¹

A punch biopsy from the liver and metastasis mass was made 25 hours after the radioiodine was administered. The concentration of radioactivity in the

TABLE I

Relative Radioactivity Measurements with Geiger Counter Tube Held Over the Midline at Various Positions and Times after Oral Administration of 1.17 mc. of I^{131}

Position	Rate Meter Reading			
	5 Min.	30 Min.	3½ Hours	24 Hours
Thyroid	13	13.5	15	15
Sternum (xiphoid)				14.5
Umbilicus	16	14.5	15	14.5
4" below umbilicus				16
Pubis				13.5
Knee				10
Ankle				8
Equidistant ¹	7	8	9	7

¹ Counter tube held at one side of thyroid at approximately the distance from thyroid to lower abdomen.

biopsy specimen (dry weight, 1.5 mg.) was slightly less than that in blood taken just before the biopsy was performed. A similar biopsy sample taken at the same time for histological examination showed partly necrotic and partly viable liver and tumor tissue. The low activity was, at this time, assumed to be due to the biopsy having been taken from an inactive portion of the metastatic mass. On the basis of the external measurements and the low urinary excretion, a second dose was administered.

Twelve millicuries of I^{131} were given orally to the subject on February 24, 1948. The external measurements at 24 hours after the radioiodine had been given followed the same general pattern found in the earlier study. After the second dose, however, the Geiger counter was in proper working condition

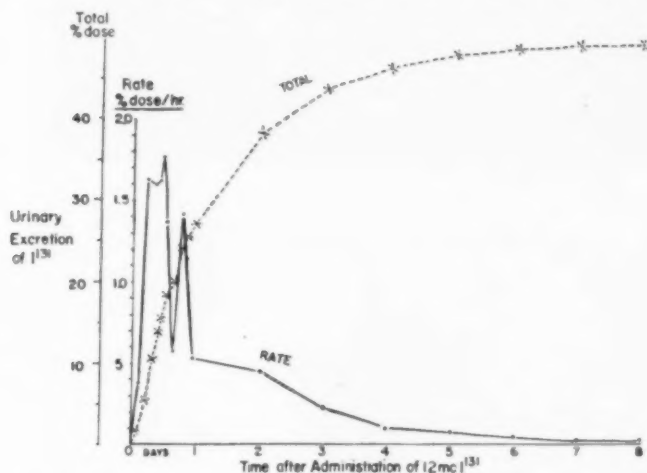


Fig. 3. Urinary excretion of I^{131} following oral administration of 12 mc. Data shown have been increased to correct for radioactive decay since the time of administration.

and it was possible to continue the external measurements for some time. The data are shown in table 2. The area of the abdomen was found to lose radioactivity at approximately the same rate as the plasma and urine, in marked contrast to the prolonged retention shown by the thyroid. A catheterization showed a residual urine volume of only 5 ml.

A search with a lead shielded counter tube failed to show any sharp concentrations of activity in small areas outside of the thyroid, though at 24 hours a weak maximum could be demonstrated over the third lumbar vertebra. This area of relatively concentrated activity may have been due either to a small amount of urine in the bladder or to the metastases found in this area at autopsy.

The blood and urine measurements, shown in figures 1 and 3, follow the same general pattern observed in the preliminary study. The excretion studies indicate a higher retention of radioiodine than normal.

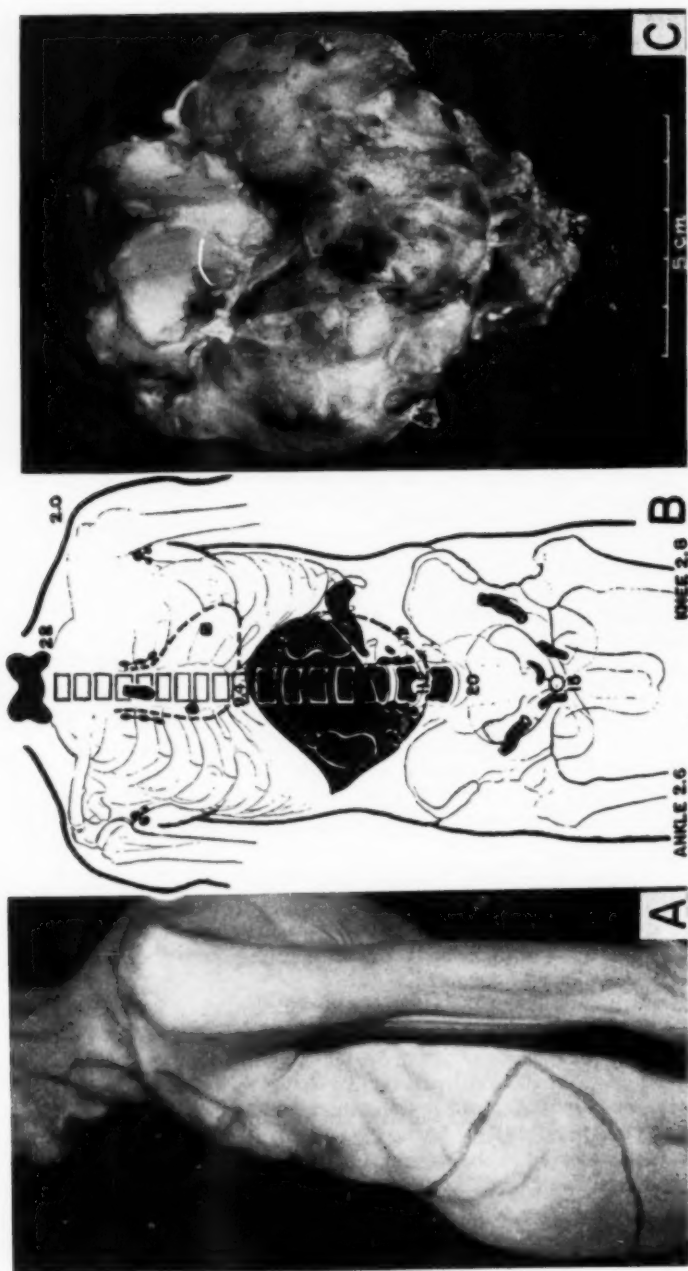


FIG. 4. A. Photograph of patient showing outline of thyroid gland and liver. B. Distribution of tumor in the body. The dark areas represent tumor found at autopsy. The figures are the external Geiger counter measurements made 24 hours after the oral administration of 12 mc. of ^{131}I . C. Primary thyroid carcinoma.

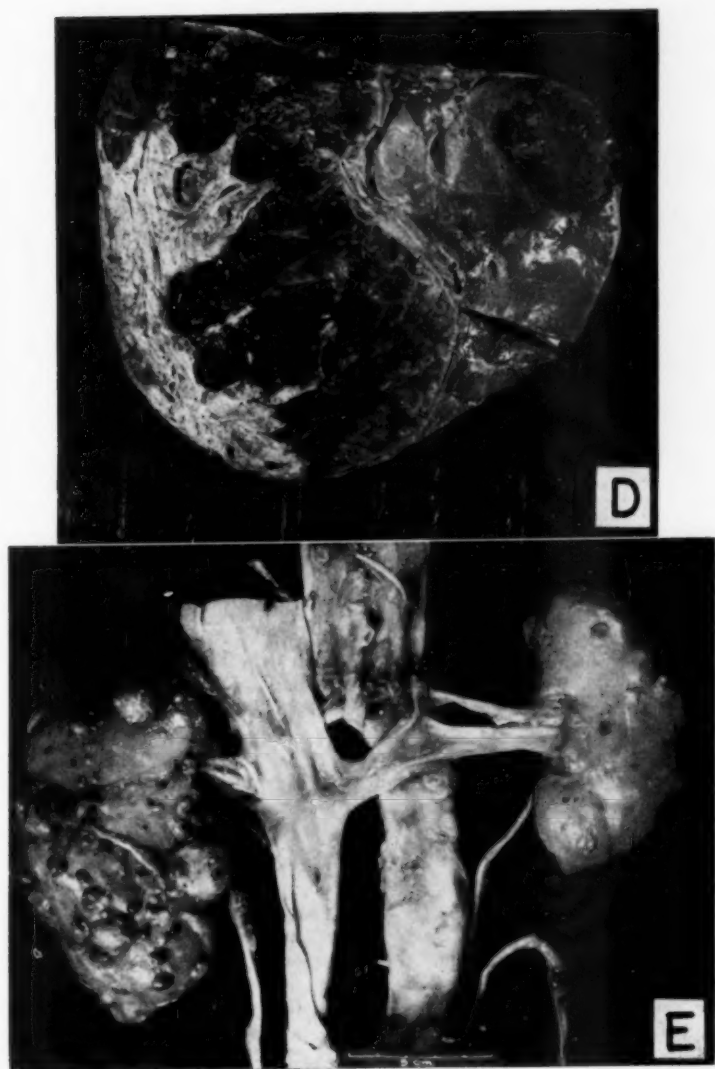


FIG. 4. D. Liver with hemorrhagic metastases. E. Kidneys with metastases.

TABLE II

Radioactivity Measurements with Geiger Counter Tube Held Over the Midline at Various Positions and Times after Oral Administration of 12 mc. of I^{131}

Position	Milliroentgens per Hour*			
	24 Hours	3 Days	7 Days	15 Days
Thyroid	22	13	15	3.7
Sternum (xiphoid)	9.4	3.0	1.4	.73
Umbilicus	11.2	3.4	1.1	.62
4" below umbilicus	20	5.3	1.3	.62
Pubis	15	4.8	0.93	.47
Knee	2.8	0.77	0.31	.20
Ankle	2.6	0.55	0.31	.15
Equidistant ¹	2.0			.22

* Corrected to time of administration.

¹ Counter tube held at one side of thyroid at approximately the distance from thyroid to lower abdomen.

A punch biopsy of the liver was taken seven days after the radioiodine had been given. The radioactivity measurements obtained on the sample (1 mg.) were not significantly above background under the conditions employed for the measurements, but a very faint radioautograph was obtained after several weeks' exposure of x-ray film to the cut surface of the paraffin block containing the specimen.

A specimen of thyroid obtained by biopsy on the seventh day showed a clear separation between a white fibrous-appearing portion and a dark reddish-brown section, which were found to contain 5.7×10^{-2} and 8.0×10^{-4} per cent of the dose per gram (wet weight), respectively. A blood sample taken just before the biopsy contained 1.9×10^{-4} per cent of the dose per gram. A very rough calibration of the survey meter in terms of millicuries indicated that on the seventh day the external radiation from the thyroid corresponded to about a tenth of the dose. To account for this fraction, about 200 grams of tissue containing radioiodine in the concentration found in the white fibrous portion of the biopsy specimen would be required. The thyroid at autopsy weighed 145 grams, and it seems probable that some portions of the thyroid attained a higher concentration of radioiodine than that shown by the biopsy specimen.

Rough calculations indicate that portions of the thyroid containing concentrations of radioiodine similar to that found in the most active section of the biopsy specimen received beta radiation of about 1000 to 2000 rep (roentgen equivalents, physical). The section taken for histological and radioautographic examination showed no separate areas which could be correlated with the white and the red-brown portions of the thyroid tissue used for chemical analysis. The radioautograph (figure 5E) showed little, if any, activity in the tumor cells themselves, exposure of the film occurring primarily over the bands of connective tissue, with the most intense exposures apparently corresponding to colloid-filled acini incorporated in the connective tissue or tumor tissue.

By the seventh day after the administration, when the biopsies were made, half of the dose had been excreted in the urine, and about 0.5 per cent was present in the blood. The rough calculations made above indicated that about one-tenth of the dose was present in the thyroid, leaving around four-tenths as the calculated

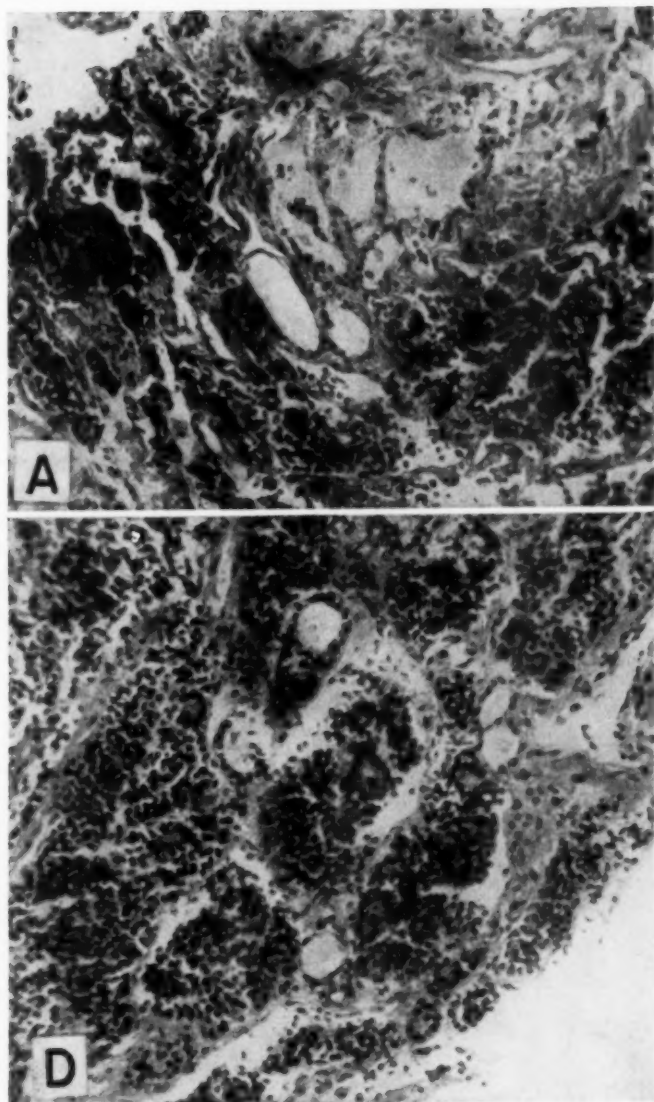


FIG. 5. A and D. See part E for legend.

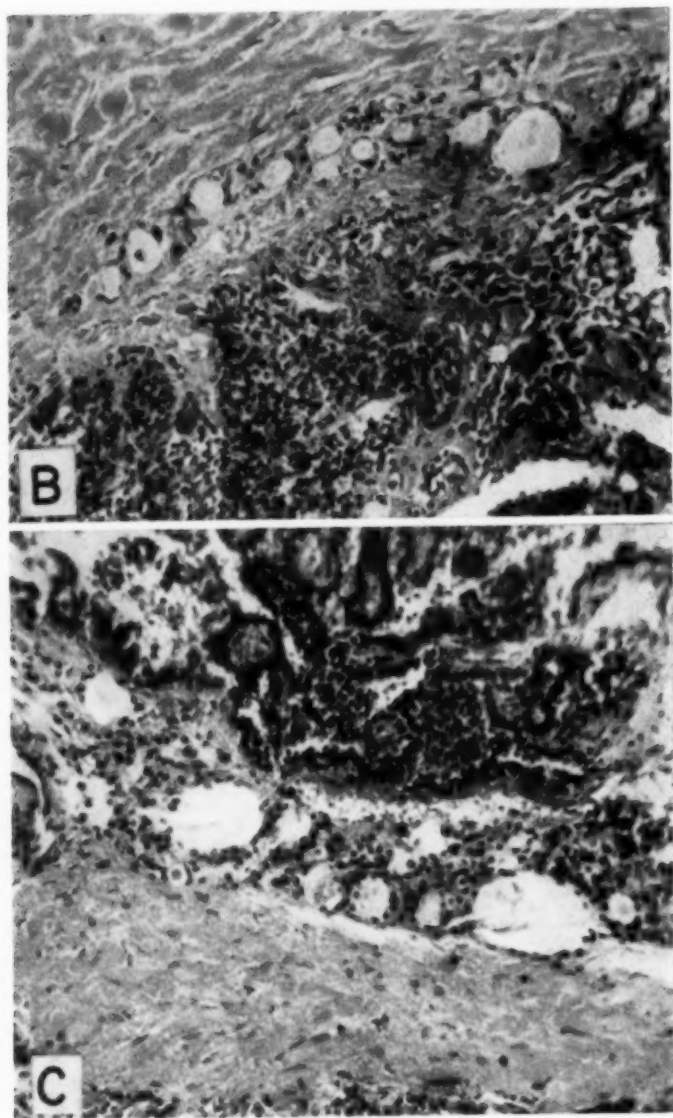


FIG. 5. B and C. See part E for legend.

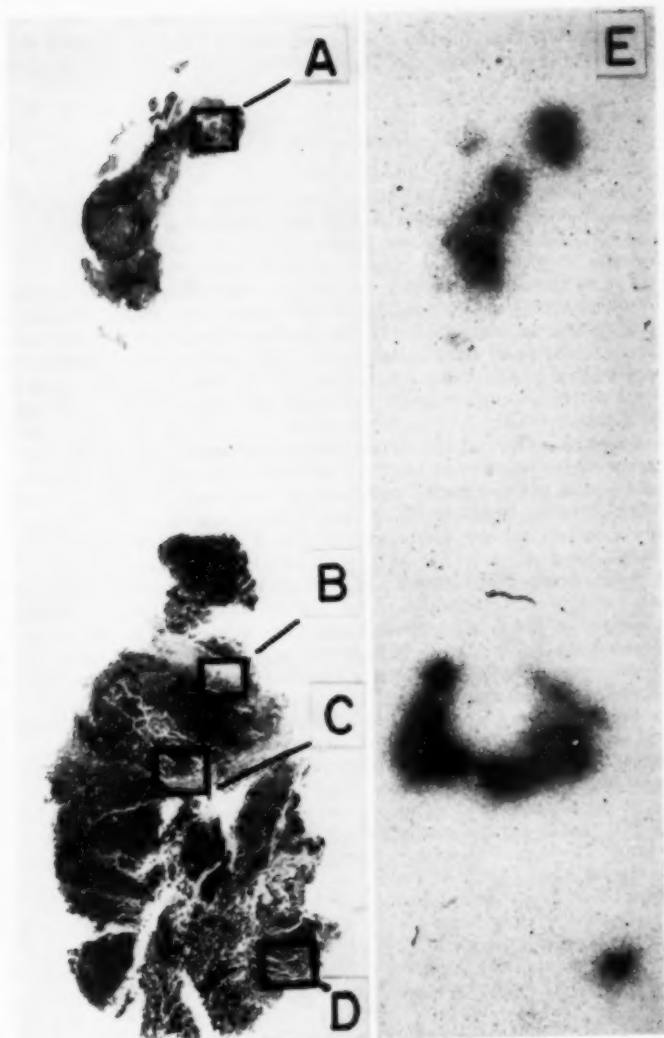


FIG. 5. Radioautograph of biopsy from the thyroid gland (E): Radioactivity corresponds to colloid containing thyroid acini incorporated within fibrous septa (B, C) and within tumor tissue (A, D).

content of the rest of the body (or in the feces, which were not collected, see discussion). Thus the general pattern of the external measurements and the excretion and biopsy data gave the impression that a large mass of tissue in the abdomen had a slight ability to concentrate iodine but could not retain it as long as the thyroid.

AUTOPSY REPORT

The body was that of a markedly cachectic 55 year old white male who measured 167 cm. and weighed 45 kilos. Radioactivity could not be demonstrated with a Geiger counter at any point over the body and gross tissue specimens did not contain enough radioiodine for accurate measurement by the technic employed. The anterior aspect of the neck was deeply pigmented from deep x-ray therapy.

The midline abdominal fat was considerably reduced and marked wasting of the pectoral muscles was seen. A small gray-white tumor nodule was present between the peritoneum and the musculature of the anterior abdominal wall. On section, its cut surface revealed many focal hemorrhages. The liver extended 20 cm. below the costal margin at the midclavicular line. The right and left diaphragmatic leaves were at the level of the fourth rib and third interspace respectively. They were considerably thinned.

The posterior surface of the sternal plate demonstrated gray-white and hemorrhagic tumor nodule clusters at the third and fourth costochondral junctions. The nodules cut with a gritty sensation and their sectioned surfaces were a soft dark red and a firmer glistening gray-white. The pleural cavities contained no excess of fluid. Firm adhesions between the diaphragmatic surface of the right lung and the diaphragm were noted.

The heart weighed 210 grams. Serous atrophy of the subepicardial fat was prominent. A 0.4 cm. gray-white tumor nodule was seen subepicardially on the anterior surface of the visceral pericardium. The mitral and aortic valves demonstrated atherosclerotic changes. The myocardium was a deep brown and irregularly streaked with gray-white. A minute gray-white tumor nodule was seen in the posterior wall of the left ventricle.

The supravascular portion of the aorta was characterized by a longitudinal wrinkling, considerable thickening and moderately severe atheromatous deposits. This process involved the remainder of the aorta and the latter deposits were more pronounced in the descending portions.

The epiglottis and larynx were grossly normal. The right and left lungs weighed 1000 and 750 grams respectively. Emphysematous blebs were seen in both apical areas. The sectioned surfaces exhibited a severe edema and hyperemia.

The thyroid gland (figure 4C) weighed 145 grams and compressed the esophagus. It was of an irregular nodular character and on section the nodules were glistening red and red-purple. Gray-white fibrous strands produced a lobular pattern and firm yellow necrotic zones were interspersed throughout.

The liver (figure 4D) weighed 6500 grams. Adhesions between its superior surface and the right diaphragm were noted. The right lobe was completely replaced by lobulated red and gray-white metastases. Protruding from the surface of the left lobe was a dark-red tumor nodule 6 cm. in diameter. The sectioned surfaces of these were occupied by central gelatinous dark-red and soft red-purple zones that were irregularly separated by bands of gray-purple fibrous tissue. The margins presented wide areas of a laminated yellow-opaque necrotic tissue. The uninvolved parenchyma of the left lobe was light tan and the lobular pattern was distinct. The central veins were occasionally exaggerated.

The gall bladder contained black mucoid bile and a black sand-like substance.

The spleen weighed 260 grams and its sectioned surface was reddish purple and fibrotic.

The right and left kidneys (figure 4E) weighed 175 and 75 grams respectively. Tumor nodules of gray-white, yellow and reddish-purple studded their surfaces and involved both cortex and medulla.

The adrenal glands were almost entirely replaced by gray-white and dark-red tumor.

The pancreas was atrophic, infiltrated by fat and contained nodules of gray-white tumor.

The esophagus was narrowed just beyond its origin. Tumor metastases were present in the submucosa of the ileum and the submucosa, muscularis and serosa of the sigmoid colon.

The lymph nodes in both axillae, para-tracheal, and para-aortic areas, mesentery and pelvis were involved by gray-white and hemorrhagic metastases. A hemorrhagic neoplastic lymph node was adherent to the left ureter at its lower one-third.

The bone marrow of the thoracic and lumbar vertebrae was irregularly replaced by gray-white sclerotic tissue. Other areas were dark red.

The right middle fossae of the skull revealed two hemorrhagic tumor nodules extending from the dura over the squama of the temporal bone into the temporal lobe. Projecting from the left internal acoustic meatus was a smaller similar nodule.

The brain presented moderate convolitional atrophy of the frontal and parietal lobes. A cavity which was almost a perfect cast of the previously described dural tumor was present in the right temporal lobe. Another nodule was located beneath the arachnoid of the lateral border of the right superior semilunar lobule of the cerebellum. On section it was of a hemorrhagic semifluid character.

The distribution of tumor in the body is shown in figure 4B together with the external Geiger counter measurements made 24 hours after administering 12 mc. of radioiodine.

Microscopic (figure 6): The thyroid is almost completely replaced by papillary adenocarcinoma of different patterns. The cells are most commonly arranged in an orderly cuboidal columnar character and are arrayed in a single row on a gentle connective tissue papillary stalk (figure 6A). The cuboidal cells are often arranged in solid cords separated from each other by capillary channels (figure 6B). Alveolar patterns are also occasionally seen (figure 6B). Solid nests and sheets of small carcinoma cells may also be observed (figure 6C). Dense bands of hyalinized collagenous tissue course throughout all and frequently incorporate compressed thyroid acini whose lumens contain pink colloid material. Most of the radioactivity as shown by radioautographs (e.g. figure 5) appears to lie in these bands (figure 5B, C). In some cases very dark spots in the radioautograph could be correlated with these acini buried within tumor tissue (figure 5A, D). Areas of hemorrhage are prominent. Blood vessels and lymphatics contain tumor. In some foci where degenerative changes are predominant the tumor tissue appears to be a series of dilated vascular channels between collapsed and degenerate forms of carcinoma cells (figure 6C).

Sections of the myocardium, liver, kidney, adrenal gland, lymph nodes, ileum, sigmoid colon, dura and bone marrow reveal metastatic tumor of a papillary adenomatous, follicular and solid character. Extensive areas of hemorrhage and necrosis are prominent features. The bone marrow is often of an osteosclerotic nature. No colloid formation can be demonstrated in either the primary or metastatic carcinoma.

Anatomic Diagnosis: Papillary adenocarcinoma of thyroid gland with metastases to regional and distant lymph nodes, myocardium, liver, kidneys, adrenal glands, small and large intestines, peritoneum, posterior aspect of sternum, lumbar and thoracic vertebrae, dura mater, cerebellum.

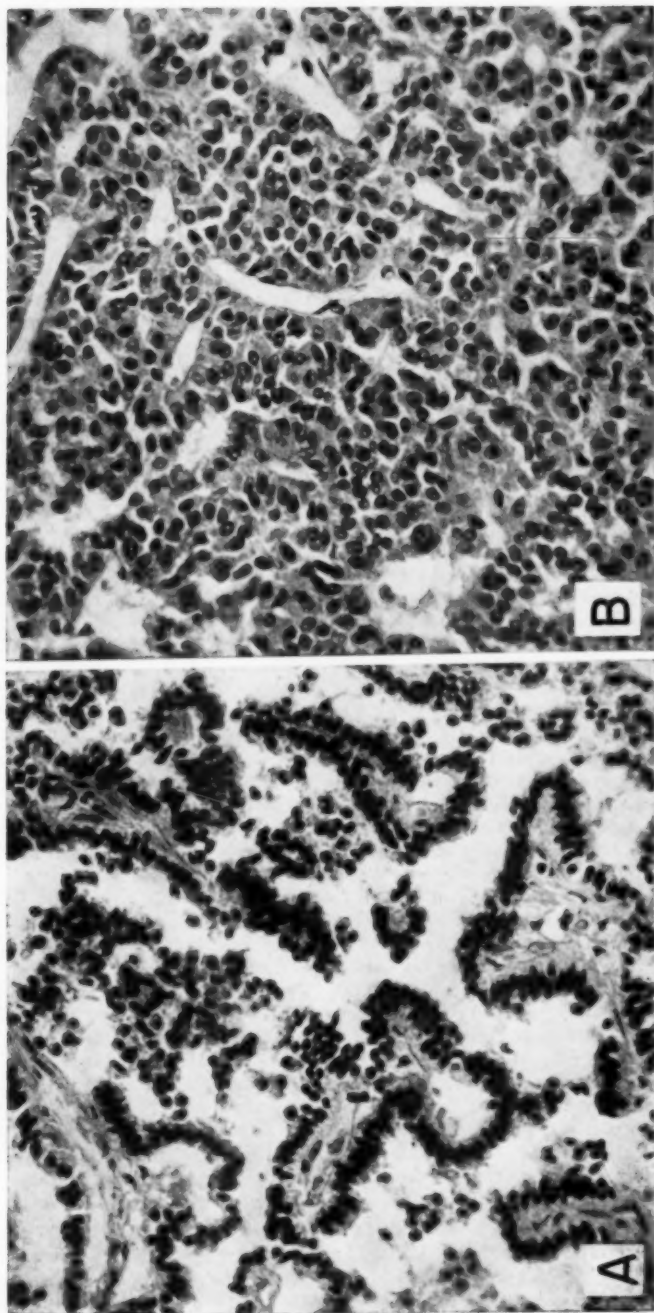


FIG. 6. Histologic variations observed in this carcinoma of the thyroid. A. Papillary. B. Simplex and alveolar.

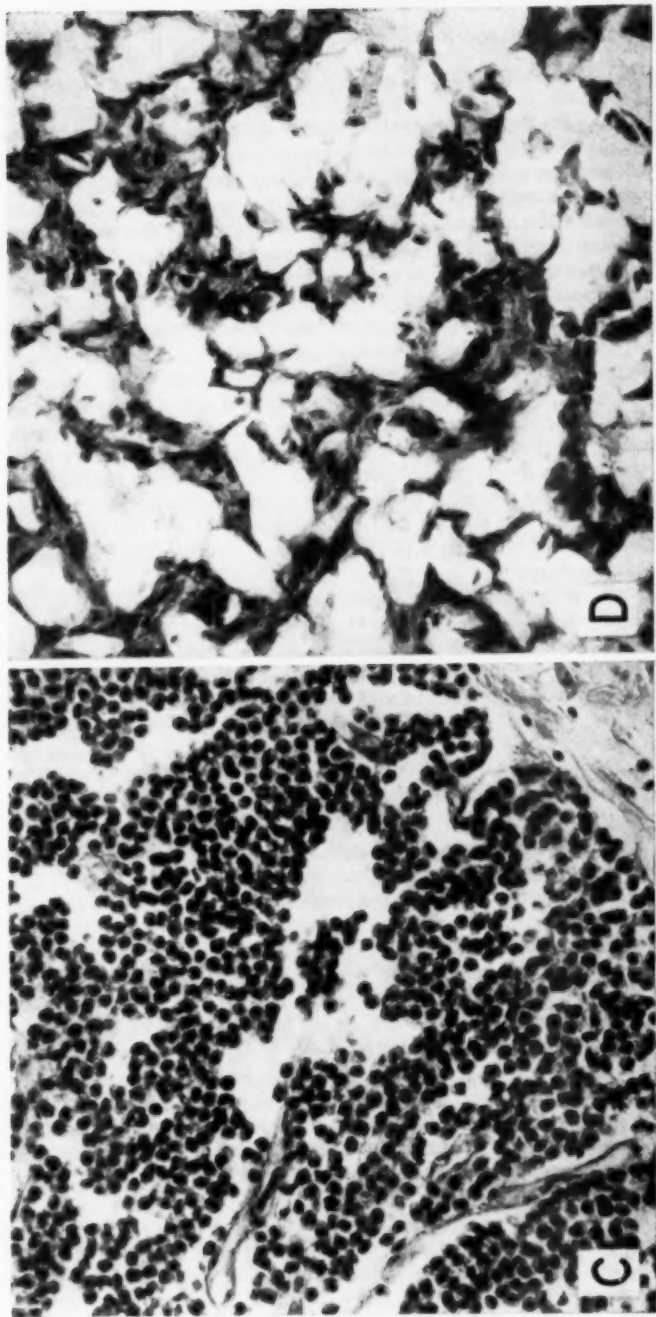


FIG. 6. Histologic variations observed in this carcinoma of the thyroid. C. Solid small-cell type. D. Vascularization and degeneration.

DISCUSSION

The ability of the thyroid adenocarcinoma of the patient presented here to concentrate iodine to a slight degree was suspected on the basis of indirect evidence but was not unequivocally demonstrated in biopsy specimens.

The external radioactivity measurements in the lower abdominal region were of the same order of magnitude as those over the thyroid 24 hours after the radioiodine had been given. Subsequently, this area was found to lose radioactivity at approximately the same rate as urine and plasma, in contrast to the prolonged retention exhibited by the thyroid.

Frantz et al.⁴ obtained moderate counts over the abdomen in their subject for several days and assumed that this was due to residual unabsorbed iodine in the abdominal organs or to the large amount of blood subtended by the counter in this region. They did not mention the possibility of radioactivity in the bladder but presumably the subject urinated before the measurements. A concentration of radioactivity in the abdomen is apparently not routinely found, for a series of patients studied by Morton²² showed similar Geiger counter readings over the abdomen and over the extended elbow within a few hours after ingestion of radioiodine. It is of interest that, as in the case presented here, the patient reported by Frantz et al.⁴ was found to have extensive metastases in the abdominal region at the time of autopsy.

In early investigations it was shown that radioiodine administered orally to human subjects was absorbed rapidly²³ and that fecal excretion accounted for a very small fraction of the dose²⁴; thus it seems improbable that the initially high readings in the abdomen were due to unabsorbed radioiodine in the intestine.

In the present instance the abdominal readings 24 hours after the radioiodine administration, when corrected for radiation from the thyroid region, were higher than would have been obtained from all the blood in the body collected in a pool directly under the counter. Similarly, residual urine volumes of about 300 ml. and 1200 ml. would have been required if the bladder content were to have accounted for the radiation from the abdomen at 24 hours and seven days, respectively, after administration of the isotope. The average daily urine volume of this patient was 600 ml., and the residual urine volume 5 ml.

Failure to find significant amounts of radioiodine in the two liver biopsy specimens may mean only that these milligram samples were not representative of the average metastasis mass. Marinelli et al.¹⁰ as a result of their studies state that despite the rather close relationship between histopathological structure of the thyroid tumors and radioiodine pick-up, a clean-cut decision of the advisability of radioiodine therapy cannot be made on the basis of a limited biopsy since such a specimen may not reveal the more favorable histopathologic patterns that may be present. In some of their cases which gave positive radioautographs there were portions of tumor that gave no evidence of ability to pick up radioiodine. They state that the follicular structure is a more favorable type than the papillary adenocarcinoma for the uptake of radioiodine. It is to be recalled that the microscopic studies of autopsy specimens in the case reported here indicated follicular as well as papillary histologic structure.

Seidlin et al.⁶ observed a rapid loss of radioiodine from the skull and femur lesions of their subject after the first day. Taurog et al.²⁵ demonstrated that the thyroids of rats treated with propylthiouracil retained the ability to concentrate

inorganic iodine but lost the ability to convert it to organic form. After a dose of radioiodine, then, these treated thyroids rapidly pick up a relatively low amount of radioactivity and then lose it at a much more rapid rate than that shown by the normal thyroid. By analogy, it seems conceivable that some types of thyroid tumor might retain only part of the iodine-concentrating mechanism and thus give curves of radioiodine pick-up and loss differing considerably from that shown by uninvolved thyroid tissue.

It was planned to continue radioiodine therapy in this patient as a method of controlling his symptoms of thyrotoxicosis and to determine whether the metastases might pick up increasing amounts of radioiodine as the amount of normal thyroid tissue decreased. Even if the tumor had developed a marked ability to concentrate iodine, however, it seems improbable that the several kilograms of tumor tissue present in the body could have been destroyed by radioiodine without using dosages so high as to cause serious damage to the kidney or other radio-sensitive tissues.

SUMMARY

A case of adenocarcinoma of the thyroid with evidence of hyperthyroidism and metastases to the liver, kidneys, bone and other organs was observed following x-radiation and radioiodine administration.

No therapeutically effective concentrations of radioiodine could be demonstrated in the metastases.

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FATAL APLASTIC ANEMIA OCCURRING DURING ANTICON- VULSANT THERAPY: PROBABLE IDIOSYNCRASY TO PHENURONE *

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A FATAL case of aplastic anemia has recently been observed in which idiosyncrasy to phenurone (acetylurea) appears to have been the cause or precipitating factor. Phenurone shows considerable promise in the treatment of epilepsy¹ and is being used with increasing frequency in selected cases. The observation that severe bone marrow depression may occur during its use seems worthy of note.

CASE REPORT

A 33-year-old white married farmer had been in good general health until shortly after discharge from the Army in 1945, when he began to have recurrent epileptic seizures. There was no history of previous convulsive attacks or head injury. Subsequent thorough diagnostic studies at the Veterans Administration Hospital, Columbia, South Carolina, and at the National Veterans Epilepsy Center, Framingham,

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From the Medical Service of the Veterans Administration Hospital, Columbia, South Carolina, Dr. S. L. Zimmerman, Chief. Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Massachusetts, failed to demonstrate evidence of an acquired organic lesion and the patient was considered to have idiopathic epilepsy. The seizures were usually preceded by a cry and rotation of the head and eyes to the left, with the right hand occasionally raised before the face. These focal movements which heralded the onset of a generalized convulsive seizure also occurred with great frequency as isolated phenomena, sometimes as often as 30 or 40 times a day. These brief minor seizures were persistent in spite of medication which controlled the grand mal attacks fairly well. In an effort to stop them several anticonvulsant drugs were used, either singly or in combination, for varying periods of time. The dosage and duration of treatment with these drugs are indicated in table 1.

TABLE 1

Anticonvulsant Drugs Employed in the Treatment of Patient. All medications except as noted were administered by the oral route. For comparison it should be noted that blood counts remained normal at least through 11/29/49 and were first found to be abnormally low on 2/10/49, with symptoms of aplastic anemia appearing on 2/20/49

Preparation	Dates of Administration	Duration	Range of Daily Dosage		Approximate Total Dose
			gm.	mg./kg.	gm.
Phenobarbital	9/12/46-5/10/48	602 days	0.045-0.12	0.75-2.0	46.8*
Dilantin sodium	9/12/46-2/27/49	889 days	0.1-0.6	1.67-10.0	288.3
Mesantoin	4/12/48-8/27/48	126 days	0.1-1.0	1.67-16.7	66.1
Phenurone	7/27/48-12/13/48				
	1/10/49-2/21/49	180 days	0.5-3.0	8.33-50.0	425.0
3,3-phenylethyl-2-piperidone	10/19/48-0/27/48	9 days	1.5-2.5	25.0-41.7	18.5
N-methyl-3,3-phenylethyl-2-piperidone	11/6/48-12/13/48	37 days	0.6-1.1	10.0-18.3	34.3

* Represents continuous oral medication, exclusive of occasional parenteral doses.

Phenobarbital and dilantin sodium were the first drugs to be used. The former was given continuously from September 1946 until May 1948, and again during the terminal illness. In addition, many supplementary parenteral injections of sodium phenobarbital were administered during and after seizures. Dilantin sodium was employed almost without interruption from September 1946 until the onset of the final illness over two years later. During the months of April, June, July, and August of 1948, the patient received mesantoin in daily doses up to 1.0 gm. On July 27, 1948, phenurone was started in initial daily doses of 0.5 gm. and gradually substituted for mesantoin. The latter preparation was finally stopped on August 27, after which phenurone was administered in an acceptable full daily dose of 3.0 gm. In view of continuing focal seizures, another anti-convulsant drug having the structural formula 3,3-phenylethyl-2-piperidone was added to the regimen on October 19, but discontinued nine days later without apparent effect. On November 6 a related compound (differing only by the addition of a methyl group to the heterocyclic piperidone ring) was added and continued during the ensuing 31 days. The patient spent the greater portion of 1948 at the National Veterans Epilepsy Center, where the above drugs were administered under close supervision. No toxic effects were noted except gingival hypertrophy and slight osteoporosis of the mandible, attributable to dilantin sodium. The hemoglobin level ranged from 12.6 to 15.0 gm. per 100 ml., with corresponding erythrocyte counts. The total leukocyte count varied from 4,150 per cu. mm. to 12,600 per cu. mm., the latter value representing slight leukocytosis during an intercurrent

upper respiratory infection. Normal differential counts were noted. The last normal blood counts were obtained on November 27 and 29, 1948. The patient was discharged from the Center shortly afterward, on December 6, at his own insistence. Upon arriving at home, he continued the combined use of dilantin sodium, phenurone, and N-methyl-3,3-phenylethyl-2-piperidone for a week and then discontinued the latter two drugs on December 13. However, the seizures were apparently not well controlled by dilantin sodium alone and began to increase in frequency and severity. The use of phenurone was accordingly resumed on January 10, 1949, and 60.0 gm. were taken during the next 42 days, indicating irregular dosage. The patient received blood counts at a local health department laboratory during this period.

On February 20, 1949, the patient became aware of insidiously developing weakness, drowsiness, anorexia, and general malaise. On the following day he noticed a sore throat with slight oozing of blood from the nose and mouth. Three days later the nose and prepuce became red, swollen, and tender. Symptoms progressed rapidly, with increasing weakness and prostration. He was admitted to the Veterans Administration Hospital, Columbia, South Carolina, on February 26, in critical condition. Upon arrival, he was able to give a fairly coherent account of his illness. Details of previous therapy were obtained from the hospital records and from relatives. Phenurone had been stopped on February 21, while dilantin sodium had been continued through the day of admission. There was no evidence of accidental or intentional over-dosage. The use of other remedies was denied. There was no history of exposure to toxic industrial or agricultural chemicals, or to irradiation. Other members of the family were not similarly affected.

Examination on admission showed a slender, poorly nourished, young white man weighing approximately 60 kg. The oral temperature was elevated to 103° F. Tachycardia was present and the blood pressure was 100/62 mm. Hg. The skin was sallow and small ecchymoses were noted over the right shoulder girdle. The mucous membranes were pale with petechial hemorrhages of the palate and nasopharynx. The tonsils were enlarged and covered with a hemorrhagic exudate. Fresh blood oozed from the nose and gum margins. Acute balanitis with superficial ulceration and bleeding about the coronal sulcus was noted. The anterior cervical, axillary, epitrochlear, and inguinal lymph nodes were barely palpable, discrete, and nontender. The spleen and liver were not felt and no localized skeletal tenderness was found. The examination was otherwise unremarkable.

Initial blood studies showed an erythrocyte count of 3,000,000 per cu. mm., hemoglobin level of 9.5 gm. per 100 ml., and an hematocrit of 31, the corpuscular constants being within normal range. A direct platelet count of 95,000 per cu. mm. was obtained. The leukocyte count was 3,100 per cu. mm. with the following differential count (200 cells):

Neutrophiles, segmented	1%
Neutrophiles, band	3%
Eosinophiles, segmented	3%
Monocytes	1.5%
Lymphocytes, large and small	87%
Degenerated leukocytes	4.5%

Erythrocytes were of normal appearance on the stained blood film, without anisocytosis, poikilocytosis, basophilia, or significant hypochromia. Toxic granulation of the few remaining neutrophils was noted occasionally. Platelets were rarely seen. No nucleated red cells, myelocytes, blast cells, or malaria parasites were found. On sternal marrow aspiration a prompt flow of sinusoidal blood occurred. No marrow particles were visible grossly and on microscopic examination the films resembled those of the peripheral blood. A second puncture was not attempted. The

trend of the blood counts obtained during the hospital course is shown in table 2. Soon after admission it was found that certain blood counts had been made at a local health department laboratory on February 10, at which time an erythrocyte count of 4,000,000 per cu. mm., a hemoglobin level of "80 per cent," and a leukocyte count of 3,800,000 per cu. mm. were stated to have been present. The last value was evidently reported in error and an actual count of 3,800 per cu. mm. is assumed. The suggestively low counts indicate depression of the cellular elements of the bone marrow at least 10 days prior to onset of toxic symptoms.

TABLE II

Trend of Hemoglobin Level, Erythrocyte Count, and Leukocyte Count during the Hospital Course. Hemoglobin is expressed as gm. per 100 ml. Cell counts are expressed as absolute numbers per cu. mm.

Date	Hemoglobin	Erythrocytes	Total Leukocytes	Neutrophils	Eosinophiles	Mono-cytes	Lymphocytes
2/27/49	9.5 gm.	3,000,000	3,100	124	93	47	2,697 (87%)
2/28/49	9.2 gm.	3,250,000	3,300				2,522 (97%)
3/ 2/49	10.5 gm.	3,500,000	2,600	78			2,821 (91%)
3/ 3/49	11.8 gm.	3,800,000	3,100	155	62	62	2,640 (88%)
3/ 4/49	12.0 gm.	4,000,000	3,000	360			2,350 (94%)
3/ 5/49	12.8 gm.	4,350,000	2,500	150			2,470 (95%)
3/ 7/49	14.0 gm.	4,950,000	2,600	130			3,264 (96%)
3/ 8/49	14.0 gm.	4,600,000	3,400	136			2,037 (97%)
3/ 9/49	14.0 gm.	4,500,000	2,000	63			1,740 (87%)
3/10/49	14.2 gm.	4,600,000	2,000	260		14	1,288 (92%)
3/11/49	13.5 gm.	4,330,000	1,400	98			784 (98%)
3/12/49	13.5 gm.	4,700,000	800	16			

Urinalysis showed slight proteinuria and the presence of moderate numbers of erythrocytes in the sediment. The Kahn test was negative. Total plasma protein was 5.76 gm. per 100 ml., with 3.06 gm. albumin and 2.70 gm. globulin. Serum bilirubin and urinary urobilinogen were within normal limits. Bromsulfalein excretion and prothrombin activity were slightly depressed. Other hepatic function tests were normal. Blood cultures and agglutinations were not done. Roentgen-ray examination of the chest on admission was normal.

Ten whole blood transfusions were administered during the course of the illness. Rise in the erythrocyte count and hemoglobin level toward normal values was noted, but leukocyte and platelet counts remained low. Procaine-penicillin G in aqueous suspension was administered parenterally and was probably responsible for transient improvement and subsidence of the nasal cellulitis and balanitis within the first few days of hospitalization. Pentose nucleotide, crude liver extract, and synthetic vitamin K were also given parenterally, but without noticeable effect. Epileptic seizures were suppressed by the use of phenobarbital, but persisted. All other anticonvulsant medication was withheld. In spite of this regimen, the general course was downward. High, continuous fever was present. The patient complained of increasing weakness, malaise, anorexia, dysphagia, and nausea with occasional vomiting. Dark liquid feces were passed. Ecchymoses continued to develop, particularly about the sites of parenteral injection. The patient lapsed into coma on the fifteenth hospital day and died 12 hours later on March 13, 1949. Permission for autopsy could not be obtained.

COMMENT

It is assumed that aplastic anemia developed in this instance because of idiosyncrasy to one of the anticonvulsant drugs employed, namely phenobarbital.

dilantin sodium, mesantoin, phenurone, or one of the two piperidones. The first three can probably be excluded in this case. Phenobarbital and dilantin sodium had each been used for over two years without serious side-effects and neither would be expected to produce aplastic anemia. Mesantoin is known to produce depression of hematopoiesis occasionally, but it had been discontinued for 175 days before the onset of symptoms and blood counts were known to have remained normal for at least 90 days after cessation of treatment with this drug. In regard to the possible rôle played by 3,3-phenylethyl-2-piperidone, one notes that it was administered for nine days, after which 115 days elapsed before the development of symptoms. Blood counts remained normal for at least 30 days after the drug was stopped. It, too, can probably be excluded from further consideration. Phenurone, on the other hand, was administered for a period of 180 days and was continued through the first day of the final illness. The total dose was approximately 425 gm., given in a daily dose of 3.0 gm., or about 50 mg./kg. for the last five months of administration exclusive of a 28 day interruption. The weight of evidence seems to point to phenurone as the agent responsible for the development of aplastic anemia in this case, but its incrimination is rendered uncertain by the fact that N-methyl-3,3-phenylethyl-2-piperidone was administered concomitantly over a period of 37 days terminating 16 days after the last known normal blood counts. During this time and the succeeding period required for ultimate excretion of the latter drug, bone marrow depression may conceivably have been initiated. N-methyl-3,3-phenylethyl-2-piperidone therefore cannot be entirely exonerated in the present instance. It should be noted, however, that 59 days elapsed between the cessation of treatment and the first suggestively low blood counts obtained on February 10, ten days prior to onset of symptoms. Initial studies* of acute and chronic toxicity of phenurone and each of the two piperidone derivatives in various species of experimental animals have not shown definite evidence of hematopoietic depression, although a small group of rats maintained for two weeks on 400 mg./kg. of phenurone daily was said to have shown blood counts at the lower limits of normal values. The observation of similar toxicity in human subjects has not been reported to the writers' knowledge.

In view of these relationships it seems that aplastic anemia in this instance probably followed the use of phenurone, with N-methyl-3,3-phenylethyl-2-piperidone to be regarded as a less likely cause. Until the toxic propensities of these and related compounds have been more fully recognized through further clinical experience, it is recommended that they be used with discrimination and under adequate supervision.

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* Preliminary experimental data on phenurone from the Abbott Research Laboratories, North Chicago, Illinois, and on 3,3-phenylethyl-2-piperidone ("MB236") and N-methyl-3,3-phenylethyl-2-piperidone ("MB 286") from the Maltbie Chemical Company, Newark, New Jersey, were obtained through personal communication with Dr. J. K. Merlis, National Veterans Epilepsy Center, Framingham, Massachusetts.

EDITORIAL

USES AND HAZARDS OF THE ORGANIC PHOSPHATE ANTI-CHOLINESTERASE COMPOUNDS

SEVERAL esters of phosphoric acid are potent inhibitors of the cholinesterase (ChE) enzymes which are present in practically all animal tissues, and, as a result, have important pharmacologic properties. Lange and von Krueger¹ were the first to note the high toxicity of one group of these compounds, the alkyl fluorophosphates, which includes di-isopropyl fluorophosphate (DFP) (figure 1). The effects of DFP were found to be due to its ability to inhibit ChE enzymes irreversibly,^{2,3} a property which enabled its utilization in the study of the rôle that ChE enzymes play in normal function and in disease.⁴ DFP has also been useful as a therapeutic agent in a

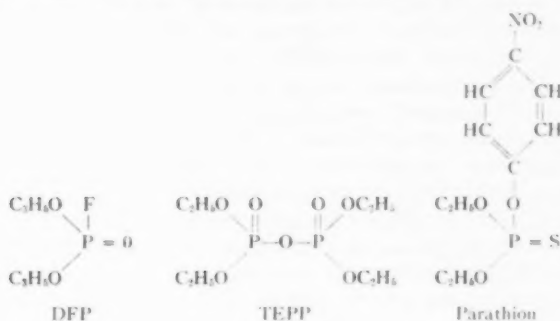


FIG. 1.

number of situations in which a cholinergic effect is desired, as in the management of abdominal distention,⁴ urinary retention, and glaucoma.⁵ Another organic phosphate compound, tetraethyl pyrophosphate (TEPP) (figure 1), has proved to be of value in the management of some patients with myasthenia gravis.⁶ The usefulness of these compounds in therapy has been limited by the relatively narrow margin between the doses which

¹ Lange, W., and von Krueger, G.: On esters of monofluorophosphoric acid, *Ber. deutsch. chem. Ges.* **65**: (Part II), 1598, 1932.

² Adrian, E. D., Feldberg, W., and Kilby, B. A.: The cholinesterase inhibiting action of fluorophosphates, *Brit. Jr. Pharmacol. and Chemotherap.* **2**: 56, 1947.

³ Mazur, A., and Bodansky, O.: The mechanism of in vitro and in vivo inhibition of cholinesterase activity by DFP, *J. Biol. Chem.* **163**: 261, 1946.

⁴ Grob, D., Lilienthal, J. L., Jr., Harvey, A. M., Jones, B. F., Langworthy, O. R., and Talbot, S. A.: The administration of DFP to man, I-IV: Effect on cholinesterase, systemic effects, effect on intestinal motility, central nervous system, and myasthenia gravis, *Bull. Johns Hopkins Hosp.* **81**: 217, 1947.

⁵ Leopold, I. H., and Comroe, J. H., Jr.: Use of DFP in treatment of glaucoma, *Arch. Ophth.* **36**: 1, 1946.

⁶ Grob, D., and Harvey, A. M.: Observations on the effects of TEPP in man and on its use in the treatment of myasthenia gravis, *Bull. Johns Hopkins Hosp.* **84**: 543, 1949.

are effective therapeutically and the doses which are toxic. The toxic effects of the organic phosphate compounds in animals of all species have led to the widespread use of some of these compounds as agricultural insecticides. These new insecticides, which are more effective than DDT, include p-nitrophenyl diethyl thionophosphate (parathion)⁷ (figure 1), TEPP,⁸ and hexaethyl tetraphosphate (HETP), the effects of which are due to TEPP, the chief active product of its initial hydrolysis.

Studies performed in experimental animals have shown that almost all the pharmacologic effects of DFP,^{2,3} TEPP,⁹ HETP,⁹ and parathion¹⁰ can be explained in terms of their anticholinesterase (antiChE) action. By inhibiting the ChE enzymes which normally hydrolyze acetylcholine, these compounds cause the accumulation of acetylcholine and resultant "cholinergic" effects. Differences in their effects can be interpreted in terms of differences in solubility, degree of antiChE action, rate of hydrolysis and detoxification, reversibility of the ChE-antiChE combination, and rate of restoration of ChE enzymes in the tissues.¹¹ Although parathion has lower antiChE activity and toxicity than TEPP, HETP, or DFP, there are at least two factors which are responsible for its greater efficiency as an insecticide. Unfortunately, these same factors are also responsible for the greater danger to man and domestic animals associated with the use of parathion. First, the rate of hydrolysis of parathion is much slower than that of the other antiChE compounds, 120 days being required for 50 per cent hydrolysis of parathion at 25° C. and pH 7. Hence once parathion has been sprayed on plants, it may remain active for weeks, in spite of contact with moisture, in contrast to TEPP, which hydrolyzes within several hours. Second, parathion is very much more soluble in lipid than in aqueous media, a property which may influence its persistence in the waxy outer layer of fruit and leaves, its absorption through the skin, and the degree of its central effects.

The organic phosphate antiChE compounds which are now in use may be absorbed through the skin, respiratory tract, conjunctivae, gastrointestinal tract, or following injection. These compounds do not produce local inflammatory changes in the skin, so that absorption by this route may be undetected until symptoms begin. Exposure may occur during the production, packaging, or handling of any of the compounds, during the spraying of insecticide preparations of parathion, TEPP, or HETP, or as a result of the harvesting or ingestion of fruit or vegetables on which they have been sprayed and which have been insufficiently weathered and washed. Ex-

⁷ Trade names of insecticide include: "Lethalaire G-54 Aerosol," "Phos Kit," "Paradust," "Vapophos," "Penphos," "Aphamite," "Genithion," "Niran," "Thiophos," and Chipman. P. A. R., Dow, Edeco 15, and Geigy Parathion.

⁸ Trade names of insecticide include "Nifos-T" and "TEPP."

⁹ Salerno, P. R., and Coon, J. M.: A pharmacologic comparison of HETP and TEPP with physostigmine, neostigmine, and DFP. *J. Pharmacol. and Exper. Therap.* **95**: 240, 1949.

¹⁰ Dubois, K. P., Doull, J., Salerno, P. R., and Coon, J. M.: Studies on the toxicity and mechanism of action of parathion. *J. Pharmacol. and Exper. Therap.* **95**: 79, 1949.

¹¹ Grob, D.: The anticholinesterase activity in vitro of the insecticide parathion. *Bull. Johns Hopkins Hosp.* **87**: 1950, in press.

posure to TEPP during its use as an insecticide has resulted in several instances of severe but not fatal intoxication, while exposure to parathion during its production and use as an insecticide has resulted in the death of at least six men, and moderate or severe, but not fatal symptoms in at least 34 men and women.^{12, 13} There have been recent reports of a larger number of fatalities and of severe intoxication due to parathion that have occurred in Brazil.

The effects of the organic phosphate antiChE compounds in man have been similar, in general, and are believed to be due almost entirely to the inhibition of the ChE enzymes in the tissues, although an additional pharmacologic effect of parathion has not been excluded. The signs and symptoms produced by these compounds include muscarine-like, nicotine-like, and central nervous system effects that are attributable to the accumulation of acetylcholine in the tissues.^{4, 6, 13} The first muscarine-like symptoms to appear are usually anorexia and nausea. These are followed by vomiting, abdominal cramps, excessive sweating and salivation, and usually some degree of pupillary constriction. If the exposure is marked, diarrhea, tenesmus, involuntary defecation and urination, pallor, pin-point non-reactive pupils, blurred vision, excessive bronchial secretion, and sometimes respiratory difficulty (suggestive of bronchoconstriction) and pulmonary edema with cyanosis follow. The blood pressure may be elevated during severe intoxication due to parathion. Of the nicotine-like effects, the earliest are muscular fasciculations in the eyelids and tongue, which may spread to the face and neck, and to the extra-ocular muscles, resulting in jerking movements of the eyes. If the exposure is marked, this is followed by generalized fasciculations and weakness, which in the most severe instances, may involve the muscles of respiration. The central nervous system effects include giddiness, restlessness, tremulousness, anxiety, headache, insomnia, and excessive dreaming. Changes in the electroencephalogram indicative of increased electrical activity of the brain have been observed. If the exposure is marked, ataxia, tremor, drowsiness, difficulty in concentrating, mental confusion, and occasionally disorientation develop. Paresthesias are common after exposure to TEPP, while changes in speech may occur after parathion. In the most severe instances this is followed by coma, with Cheyne-Stokes respiration and the disappearance of all reflexes, and then by generalized convulsions. Death has occurred in coma one to 13 hours after the onset of symptoms. The precise cause of death is not known, but contributing factors are believed to be depression of the respiratory and circulatory centers in the medulla, weakness of the muscles of respiration, and pulmonary edema.

The acute effects of the organic phosphate antiChE compounds last for 6 to 30 hours, but mild symptoms may persist for several days. Occasion-

¹² Grob, D., Garlick, W. L., Merrill, G. G., and Freimuth, H. C.: Death due to parathion, an anticholinesterase insecticide, *Ann. Int. Med.* **35**: 899, 1949.

¹³ Grob, D., Garlick, W. L., and Harvey, A. M.: The toxic effects in man of the anticholinesterase insecticide parathion, *Bull. Johns Hopkins Hosp.* **87**: 1950, in press.

ally the pupils may not return to the normal size for several weeks, probably because the antiChE compound has been sprayed or rubbed into the eyes. The only significant laboratory finding is the depression of the ChE enzymes of the blood and tissues, and the only postmortem findings are hyperemia and edema of the lungs, and sometimes of the brain and other organs. Following death due to parathion the ChE activity of the plasma and red blood cells has been found to be reduced to 14 and 22 per cent of normal, and that of the various tissues to between 22 and 88 per cent of normal.

The effects of the antiChE compounds are due to inhibition of the ChE enzymes of the nervous system, muscle, and secretory glands, and not to the coincident inhibition of the ChE enzymes of the plasma and red blood cells. However, since it is not possible to determine the ChE activity of the tissues in man during life, it is necessary to rely on the ChE activity of the plasma and red blood cells as a guide of some value in detecting absorption of the antiChE compounds and the persistence of their effects. The ChE enzyme of the plasma is more sensitive to inhibition by the antiChE compounds now in use than are the enzymes of the red blood cells, brain, or muscle, which are approximately equally sensitive to inhibition by each compound. The ChE activity of the red blood cells can be used as a rough guide to the activity of the tissue enzymes, but only if the exposure to the antiChE compound is relatively brief. If the exposure occurs over a longer period of time, this guide is less reliable, since the rate of restoration of the ChE activity of the red blood cells appears to be slower than that of the tissues in man.

The rate of restoration of the ChE enzymes following their depression by any of the antiChE compounds depends upon the reversibility of the ChE-antiChE combination, and upon the rate of regeneration of new enzyme protein. The combination between DFP and ChE enzymes is reversible for several minutes, following which the enzymes are permanently inactivated and their activity restored at rates which are compatible with the regeneration of new enzyme protein.⁴ The rate of restoration of plasma ChE (apparently by the liver) is approximately 14 per cent of original activity on the first day, 9 per cent on the second day, and 2 to 6 per cent on subsequent days until the activity has been restored to normal. The red blood cell ChE is restored at a uniform rate of approximately 1 per cent of original activity per day, which probably represents the replacement rate of the red blood cells.

The combination between TEPP or parathion and ChE enzymes is partly reversible for several hours, following which the enzymes are permanently inactivated.^{6, 11} During the first day after exposure to these compounds the rate of restoration of the ChE enzymes of the plasma and red blood cells is more rapid than following DFP, by about 10 per cent of the original activity. After the second or third day, however, these enzymes are restored at the same rate as following DFP.

Although the exact rate of restoration of the ChE enzymes of the tissues following their depression by the antiChE compounds is not known in man,

this restoration appears to occur over a period of many days, and to be slower after DFP than after TEPP or parathion. For several days after exposure to any of these compounds, during which time the ChE enzymes of the tissues have probably not yet been restored to normal, there is increased susceptibility to any repeated exposure, and cumulative effects may occur. This cumulative action is particularly dangerous because there is a fairly narrow margin between the doses of these compounds that produce symptoms and the doses that are lethal, so that little or no warning may be given of impending serious effects. The oral dose of DFP or TEPP required to produce moderate symptoms is approximately 25 mg., while the lethal oral dose of these compounds is *estimated* to be about 100 mg.¹³ The comparable toxicity of parathion and DFP for experimental animals suggests that the dose-effect relationship of parathion for man *may* approximate that of DFP. It is probable that the ChE activity of the tissues may be considerably reduced by these compounds without the appearance of any warning symptoms, while a further reduction below the level compatible with normal function may result in marked symptoms and even death.

The dangers of the organic phosphate antiChE compounds necessitate stringent precautions in their use, particularly in the case of insecticide preparations of parathion. These precautions include adequate warning labels, distribution only to properly instructed personnel, protective clothing (including gloves, goggles, and respirator), exhaust ventilation where possible, protection against wind dispersal, and careful disposal of contaminated material. Fruit, vegetables, or tobacco should be sprayed only with very dilute solutions, harvested not less than several weeks after the last spraying, and thoroughly washed prior to use. It is recommended that personnel who are exposed frequently have periodic determinations of the ChE activity of the plasma and red blood cells, and that those who develop reduction in ChE activity be removed from all exposure until this has been restored to normal, which will usually require several weeks.

Personnel contaminated with any of the organic phosphate antiChE compounds should have their clothes removed immediately and the skin washed. Atropine may be administered prophylactically. The treatment of symptoms due to the antiChE compounds relies chiefly on atropine, which has a moderate inhibitory effect on the muscarine-like, and a less striking effect on the central nervous system manifestations. Patients who have moderately severe symptoms due to the antiChE compounds have an increased tolerance for atropine, so that fairly large doses may be given. It is recommended that 2 mg. of atropine be administered intramuscularly, at hourly intervals, or more often if necessary, until signs of atropinization appear. Following this, the dose of atropine may be reduced, but its administration should be continued as long as any signs or symptoms of the antiChE compound are present. Adjuvants to atropine therapy include gastric lavage to remove any unabsorbed antiChE agent, parenteral replacement of fluids, and the administration of oxygen if needed. The occurrence

of weakness of the pharyngeal and respiratory muscles may necessitate tracheal intubation and artificial respiration. If the convulsions are severe, the careful administration of ether or a barbiturate for their amelioration may be of value. Morphine should not be administered, as its action may be potentiated by antiChE compounds.

The organic phosphate antiChE compounds, which were developed for the most part as a result of wartime research, have proved to be useful in several ways, especially as insecticides. Newer and more potent analogues are being continually developed. It is hoped that appreciation of the properties and hazards of these compounds will prevent the harmful results of their careless or indiscriminate use.

DAVID GROB

REVIEWS

Bronchiogenic Carcinoma and Adenoma, with a Chapter on Mediastinal Tumors.

By B. M. FRIED, M.D. 306 pages; 16 × 23.5 cm. The Williams & Wilkins Co., Baltimore 2, Md. 1948. Price, \$6.00.

This monograph reflects the author's wide personal experience and his individual point of view. It will therefore be of chief interest and value to the internist and the chest physician and is not particularly suitable except as a topical reference to the student, the surgeon or the general practitioner.

In disputed points the author presents fairly the views of others but also courageously states his own opinions; for example, he cites fully those who believe that carcinoma of the lung is showing an increased incidence, but also explains the reasons for his own belief that this increase is more apparent than real. He differs also with the accepted classification of epidermoid carcinoma. Human pulmonary adenomatosis, so similar to epizootic (Jaagsiekte), he believes arises from multiple centers but probably on an infectious virus basis.

The author's evident interest in the significance of hypertrophic pulmonary osteoarthropathy has led to the assignment of perhaps an undue amount of space to the discussion of this entity. However, this beautifully illustrated chapter is a real addition to the book. One might pick out for praise also the chapter on superior pulmonary sulcus tumors, with its interesting diagrams elucidating the mechanism of the accompanying neurological disturbances. Under the discussion of the laboratory methods of diagnosis, due prominence is given to the newer studies of the cytology of the bronchial secretions.

There are certain omissions which appear regrettable. Internists as well as surgeons would be appreciative of more discussion of surgical therapy, particularly of pre- and post-operative measures, and of the post-operative residual functional problems.

All in all, this is a very valuable and timely monograph by an author whose experience and opinions deserve careful consideration.

J. H. H.

The Thyroid Hormones and Their Action. 2nd ed. By G. MANSFELD, M.D., Professor of Physiology, University of Budapest; translated by Erwin Pulay, M.D. 157 pages; 16 × 25 cm. Frederick Muller, Ltd., London. 1949. Price, 24' net.

This monograph, originally published in German in 1943, brings together the investigations of thyroid physiology carried out at the University of Budapest over the last forty years. The reader acquainted with the main currents in this field in the English literature will soon find himself in unfamiliar waters. The oblique approach of Professor Mansfeld and his school comes as a shock and a surprise, doubtless a salutary experience, to those workers who adhere to the unitary concept of thyroid function.

The subject matter falls into three divisions. The first considers the relation of the thyroid gland to anemia, and especially to "pernicious anemia." The latter was produced by injecting rabbits with saponin and collargol. This was shown to respond to injections of liver, and such preparations were used to assay liver fractions. It is perhaps worth mentioning that this assay method has found no general acceptance. Recovery from this type of anemia or from that following bleeding or injections of phenylhydrazine was found to require an intact thyroid gland. One is not surprised to learn that recovery occurs more slowly in the thyroidectomized rabbit, but he

would prefer to see documentary evidence or at least be supplied with a reference when it is stated that normal rate of blood regeneration is restored by thyroid extract, but not by thyroxin. Pursuing this discrepancy, these workers postulated a "myelotropic hormone." This was subsequently isolated from the thyroid gland. Separation from thyroxin and purification are claimed, but not chemical identification. Professor Mansfeld's hope that it may be effective in human pernicious anemia seems foredoomed in view of the known ineffectiveness of thyroid extract in this disease.

In the second section there is introduced the provocative concept that thyroxin directly influences the oxidation of isolated cells but that this can be shown only under conditions of low oxygen tension, higher tensions inhibiting activity otherwise influenced by the thyroxin. For purposes of criticism one might wish to have precise information concerning the composition of the fluid phase of the Warburg cups and especially on the actual quantity of tissue employed. These findings, if confirmed, would mark a major advance in the solution of one of the most perplexing problems in thyroid physiology, the mode of action of the hormone on the cell.

Another perplexing problem to thyroid physiologists has been the latency in action of thyroid extract. From an ingenious series of experiments on denervated organs and muscles the conclusion is reached that the reason for this latency is that thyroid hormone passes first to the central nervous system via nerves, whence it finds its way to the periphery again via nerves. Some of the supporting evidence for this concept strains one's credulity. Thus testimony is cited to the effect that the antlers of a stag shot in the scrotum fail to grow on the side opposite the damaged testis.

Section III considers the problem of the "thermothyryns." The concept of "thermothyryn" arose from a consideration of the following experimental evidence. An injection of novocaine into a guinea pig causes a fall in body temperature which is antagonized by thyroxin. This antagonistic effect fails to appear in thyroidectomized guinea pigs, but reappears after transection of the spinal cord. These observations were true only when made in the wintertime. In the spring after cord transection thyroxin does not prevent the temperature fall caused by novocaine. Thyroidectomy reverses the situation and thyroid again antagonizes the novocaine. It is concluded therefore that in the spring guinea pigs produce a substance which antagonizes the peripheral effects of thyroxin and which comes from the thyroid gland. After studying a variety of extracts from the thyroid two substances were found which possessed the property of antagonizing the peripheral effects of thyroxin. These were called Thermothyryn-A and Thermothyryn-B depending on their acid or alkaline solubility. They were obtained in crystalline form but were not identified chemically. They sharply diminished the oxygen consumption of normal dogs. They were also crystallized from the blood of man and animal. Previously it had been shown that blood removed from an animal which had been overheated had the property of antagonizing the effect of thyroxin on thyroidectomized animals. It was shown that the blood of overheated animals showed an excess of thermothyryn. However, pure thermothyryn caused an increase in oxygen consumption of isolated tissues and also increased the oxygen consumption of the thyroidectomized rats. However, in the thyroidectomized rats an implantation of whole thyroid caused thermothyryn to produce a lowering of oxygen consumption. A preparation of colloid from a thyroid which contained only 50 gamma of iodine per dose reversed the thermothyryn effect in the thyroidectomized rat.

The final chapter in this section is a defense of the thesis of dysthyroidism in Graves' disease, a concept long held by many. Mansfeld theorizes that since there is no good evidence of thyroxin over-production in Graves' disease (for which abundant evidence now exists), the most tenable theory of Graves' disease is that such thyroid glands are making a normal or increased amount of thermothyryn and a reduced amount of thyroxin. If this is true, the injection of thyroid colloid should

cure Graves' disease. This was found to be the case in a single instance wherein a patient with apparent severe Graves' disease had a dramatic and immediate improvement following the subcutaneous implantation of a colloid goiter removed from an otherwise healthy patient.

From many points of view this is a remarkable book. Professor Mansfeld is a master of the uncontrolled post hoc argument and is adept at bending evidence to fit his theories. Thus, Hamilton and Soley's findings that radioactive iodine leaves a Graves' gland rapidly is quoted to support the theory that the Graves' gland is unable to store iodine and therefore is forming thyroxin slowly. Incidentally this is the only reference to radioactive iodine. What troubles one is that were he to follow his inclination and dismiss this work in its entirety he might discard some new and vital truth. It is for this reason that this work is worthy of the attention of investigators in the field.

J. B. S.

Medical Diseases of the Kidney: An Atlas and Introduction. By J. F. A. McMANUS, M.D. 176 pages; 17 × 26.5 cm. Lea and Febiger, Philadelphia. 1950. Price, \$6.00.

It is refreshing to read and enjoy an original presentation of renal diseases. Such is the experience afforded by this beautifully produced book. Dr. McManus has approached the subject from the point of view of a pathologist interested not only in structural changes but also in both the chemistry of the cell and the symptoms of the patient. He has divided his subject into acute renal failure and chronic renal failure, which in itself bears testimony to the author's clinical approach.

There is an excellent introductory section on the normal structure and physiology of the kidney. The illustrations are superb works of art: of the 160 pages of actual text, 99 are devoted entirely to photomicrographs. All of these are of the highest quality and deliver the author's message with great eloquence. Most of the sections are prepared by the recent periodic acid-Schiff's reagent technic which demonstrates clearly the renal basement membranes. It permits recognition and separation of the processes of glomerular injury in arteriosclerosis, in pyelonephritis and in glomerulonephritis; and it alone, in the author's opinion, permits recognition of certain glomerular changes diagnostic of eclampsia.

Another recent method adopted by the author is Gomori's method for demonstrating alkaline phosphatase in the renal tubule; by means of this method he shows that the "crush" kidney is diffusely involved including the proximal tubules—a point against the popular term "lower nephron nephrosis." The whole section on the "Crush Kidney" contains much that is new and stimulating.

Due recognition is given to Ellis' work, so often overlooked, and attention is drawn to the histologic similarity between the Type II nephritis of Ellis and the intercapillary glomerulosclerosis of Kimmelstiel and Wilson—suggesting that some common etiologic factor may be found.

It is clear that Dr. McManus has based this monograph on his own knowledge derived from his own experience. He has reached his conclusions about the kidney "by the long, patient and varied use of the microscope" as Malpighi did before him.

H. J. L. M.

Occupational Marks and Other Physical Signs: A Guide to Personal Identification. 1st ed. By FRANCESCO RONCHESI, M.D. 181 pages; 16 × 23.5 cm. Grune & Stratton, New York. 1948. Price, \$5.50.

As an exposition of one individual's experiences in these fields—occupations and marks—this first edition is interesting. It is small, well bound and nicely printed. The author's style is easy and he has collected many illustrations, chiefly black and white photographs. Many rare conditions are mentioned.

As a serious study of occupations and marks it is incomplete and perhaps misleading. Trades and occupations are sometimes given as specific causes of marks rather than the utensil or definitive manipulation used. Failure to emphasize nutritional factors is surprising. Eczema and psoriasis are pictured several times. Some of the picture legends are confusing. Fingerprint photography is ignored.

This book could be an addition to a library dealing with problems in forensic, industrial, or dermatologic aspects of medicine.

C. A.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Applied Medicine. By G. E. BEAUMONT, M.A., D.M., F.R.C.P., D.P.H., Physician to The Middlesex Hospital and Hospital for Diseases of the Chest, Brompton. 540 pages; 24 × 15.5 cm. 1950. The Blakiston Company, Philadelphia. Price, \$6.00.

Cardiography. By WILLIAM EVANS, M.D., D.Sc., F.R.C.P., Physician to the Cardiac Department of the London Hospital, etc. 140 pages; 25 × 16.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, \$6.75.

Chemical Developments in Thyroidology. By WILLIAM T. SALTER, M.D., Professor of Pharmacology, Yale University School of Medicine. 87 pages; 22.5 × 14.5 cm. (limp leather binding). 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$2.00.

Clinical Nutrition. Edited by NORMAN JOLLIFFE, M.D., F. F. TISDALL, M.D., and PAUL R. CANNON, M.D., for the Food and Nutrition Board of the National Research Council. 925 pages; 24.5 × 16.5 cm. 1950. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$12.00.

Conference on Problems of Aging: Transactions of the Tenth and Eleventh Conferences, February 9-10, 1948, and April 25-26, 1949. Edited by NATHAN W. SHOCK, Chief, Section on Gerontology, National Heart Institute, etc. 258 pages; 23 × 15 cm. (paper-bound). 1950. Josiah Macy, Jr. Foundation, New York. Price, \$3.75.

Factors Regulating Blood Pressure: Transactions of the Third Conference, May 5-6, 1949, New York, N. Y. Edited by B. W. ZWEIFACH and EPHRAIM SHORR, Department of Medicine, Cornell University Medical College. 280 pages; 23 × 15 cm. (paper bound). 1950. Josiah Macy, Jr. Foundation, New York. Price, \$2.55.

A Guide to General Medical Practice. By MARTIN G. VORHAUS, M.D., Attending Physician, Hospital for Joint Diseases, New York City. 244 pages; 21 × 14 cm. 1950. The Macmillan Company, New York. Price, \$3.50.

Harvey Cushing: Surgeon, Author, Artist. By ELIZABETH H. THOMSON; Foreword by JOHN F. FULTON. 347 pages; 21.5 × 14.5 cm. 1950. Henry Schuman, New York. Price, \$4.00.

History Taking. By GEORGE BLUMER, M.D. 51 pages; 19.5 × 13.5 cm. (paper-bound). 1949. Associates of the Yale Medical Library, New Haven. Price, \$1.50.

Klinische Pathologie der Blutkrankheiten. By PROF. DR. RUDOLF SCHOEN and PROF. DR. WALTER TISCHENDORF. 521 pages; 24.5 × 17.5 cm. 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 57.-

- Liver Injury: Transactions of the Eighth Conference, April 28 and 29, 1949, New York, New York.* Edited by F. W. HOFFBAUER, M.D., Department of Medicine, University of Minnesota Medical School. 164 pages; 23 × 15 cm. (paper-bound). 1950. Josiah Macy, Jr. Foundation, New York. Price, \$1.60.
- Methods in Medical Research.* Volume 2. JULIUS H. COMROE, JR., Editor-in-Chief; *Methods of Study of Bacterial Viruses:* MARK H. ADAMS, Editor; *Pulmonary Function Tests:* JULIUS H. COMROE, JR., Editor; *Assay of Hormonal Secretions:* ELEANOR H. VENNING, Editor. Governing Board: IRVINE H. PAGE, Chairman; A. C. IVY, COLIN H. MACLEOD, CARL F. SCHMIDT, EUGENE A. STEAD, DAVID L. THOMSON. 361 pages; 22.5 × 14 cm. 1950. The Year Book Publishers, Inc., Chicago. Price, \$6.50.
- The 1949 Year Book of Neurology, Psychiatry and Neurosurgery (December 1948–October, 1949).* *Neurology* edited by ROLAND P. MACKAY, M.D., Professor of Neurology, University of Illinois, etc.; *Psychiatry* edited by NOLAN D. C. LEWIS, M.D., Director, New York State Psychiatric Institute and Hospital, etc.; and *Neurosurgery* edited by PERCIVAL BAILEY, M.D., Distinguished Professor of Neurology and Neurological Surgery, University of Illinois. 668 pages; 18.5 × 12.5 cm. 1950. The Year Book Publishers, Chicago. Price, \$5.00.
- The Nose: An Experimental Study of Reactions Within the Nose in Human Subjects During Varying Life Experiences.* By THOMAS H. HOLMES, M.D., Lester N. Hofheimer Research Fellow in Medicine; HELEN GOODELL, B.S., Research Fellow in Medicine; STEWART WOLF, M.D., Associate Professor of Medicine, and HAROLD G. WOLFF, M.D., Professor of Medicine (Neurology), Cornell University Medical College; with a Foreword by WARFIELD T. LONGCOPE, M.D., Professor Emeritus of Medicine, The Johns Hopkins Medical School. 154 pages; 24 × 15.5 cm. 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$4.50.
- The Pathology of Articular and Spinal Diseases.* By DOUGLAS H. COLLINS, O.B.E., M.D. (Liverp.), Reader in Clinical Pathology in the University of Leeds, etc. 331 pages; 23 × 14.5 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, \$7.00.
- Saw-Ge-Mah (Medicine Man).* By LOUIS J. GARIEPY, M.D. 326 pages; 20.5 × 13.5 cm. 1950. Northland Press, Saint Paul, Minnesota. Price, \$3.00.
- Textbook of Bacteriology.* 2nd ed. By JOSEPH M. DOUGHERTY, A.B., M.A., Ph.D., Dean of the School of Science and Professor of Bacteriology, Villanova College, etc., and ANTHONY J. LAMBERTI, B.S., M.S., Instructor in Bacteriology and Parasitology, Temple University School of Medicine, etc. 491 pages; 25 × 17 cm. 1950. The C. V. Mosby Company, Saint Louis. Price, \$5.75.
- Treatment in Psychiatry.* 2nd ed. By OSKAR DIETHELM, M.D., Professor of Psychiatry, Cornell University Medical College, etc. 546 pages; 23.5 × 15.5 cm. 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$8.50.
- Veterans Administration Technical Bulletins—Series 10, Volume III, 1949.* 162 pages; 27 × 20.5 cm. 1950. Veterans Administration, Washington, D. C. Price; Not for sale—limited edition for distribution to VA hospitals and medical libraries.
- Water and Salt Depletion.* By H. L. MARRIOTT, C.B.E., M.D., F.R.C.P., Middlesex Hospital, London, England. 80 pages; 22 × 14.5 cm. 1950. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$2.00.

COLLEGE NEWS NOTES

THE 31ST ANNUAL SESSION, A.C.P.

The 31st Annual Session of the American College of Physicians, Boston, Mass., April 17-21, 1950, is now history. Due to the excessive growth in attendance at the Annual Meetings of the College, an attempt was made to reduce somewhat the non-member attendance at Boston for the protection of members of the College for whom the meetings are conducted and who are entitled to places in the Clinics, Panel Discussions and other program features. The registration fee of non-members was raised to \$25.00, and it was required that all non-members be sponsored in advance by members of the College. The effectiveness of this new procedure is somewhat difficult to analyze, because the number of guest physicians was reduced only from 1,471 in 1949 (New York) to 1,225 in 1950 (Boston). However, meeting room facilities in Boston were more adequate than in New York, and it is believed that non-members interfered minimally with the attendance of members at program features. The attendance for 1949 and 1950 was as follows:

	1949	1950
A.C.P. Members	2,486	2,091
Guest Physicians	1,471	1,225
Guest Non-Physicians	38	42
Exhibitors	665	591
Ladies	967	840
Total	<u>5,627</u>	<u>4,789</u>

Physicians were in attendance from every State except Nevada, from the Canal Zone, Hawaii, Puerto Rico, Canada, Cuba, Ecuador, England, Ireland, Japan, Mexico, the Netherlands, Saudi Arabia, Union of South Africa and Venezuela.

The Technical Exhibit, consisting of 129 booths and 105 separate and distinct exhibitors, was the largest and most extensive in the history of the College. All exhibits were restricted to products relevant to the practice of internal medicine or its allied specialties, and all exhibitors were admitted on invitation from the Committee on Exhibits after investigation of the firms and their products. Furthermore, each exhibit was personally inspected by each member of the Committee on Exhibits. It is felt that the Technical Exhibit of the American College of Physicians is conducted on the highest plane of any similar exhibit within the United States.

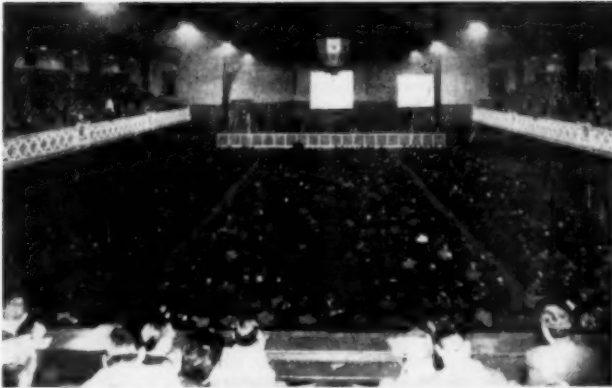
There were 20 individual Panel Discussions, and in most instances the rooms were filled to capacity. Even those Panels that usually are limited in their general appeal were attended by large numbers. For instance, the Panel on the Management of Syphilis had an attendance of 212; the Panel on Medical Aspects of Atomic Energy had an attendance of 232, and the Panel on Poliomyelitis had an attendance of 152. Some of the more popular Panels had an attendance exceeding 400.

The Clinics given in the hospitals were in most instances attended to capacity, the exception being those given at the Veterans Administration Hospitals at some distance outside of Boston, where the time element for transportation was the chief deterrent.

Televised Clinics in Color. A new feature on the program of the American College of Physicians was the television in color of medical clinics from the Massachusetts General Hospital to the auditorium. The Massachusetts General Hospital was utilized as the source of transmitting the programs, but numerous Boston hospitals presented their cases from this one place. This program proved extremely popular, and the consensus was that it is entirely practical and worth while to televise



The College Booth—Mechanics' Building.



One of the General Sessions—Grand Hall—Mechanics' Building.



Activity and Lively Interest—Technical Exhibit.

in color many of the medical clinics. Between 700 and 800 physicians attended the televised clinics daily, and this greatly relieved the pressure of attendance at the hospital clinics. Had it not been for the television program, the capacities at the hospital clinics would have been inadequate to accommodate the members. It is believed that the television program can be further improved and extended in succeeding years, and it is now planned to arrange an even more extensive television program in color at the 1951 Annual Session.

The General Sessions and Morning Lectures were attended by large numbers, reaching 3,000 at some sessions. The contributors to this part of the program, with three exceptions, were all members of the American College of Physicians, the exceptions being Dr. Karl F. Meyer, of San Francisco, the James D. Bruce Memorial Lecturer on Preventive Medicine; Dr. Edward C. Kendall, of Rochester, Minn., the John Phillips Memorial Lecturer on Cortisone, and Lord Moran, President of the Royal College of Physicians of London, who presented one address on the General Sessions program and delivered the Convocational Oration.

The report on the Convocation and the conferring of special awards follows:

The Annual Convocation

The Annual Convocation of the American College of Physicians was held in the Ballroom of the Hotel Statler, Boston, April 19, 1950. Fellowships were conferred on 300 physicians. The first Honorary Fellowship of the College was conferred upon the Right Honorable Baron Moran of Manton, President of the Royal College of Physicians of London, who delivered the Convocational Oration.

A Mastership was conferred upon Dr. Roger I. Lee, a former President of the College, "in recognition of his professional attainments and by the force of his example to younger men in the arts of medicine and his service to the College."

The John Phillips Memorial Award was conferred upon Dr. Edward C. Kendall, Professor and Head of the Section of Biochemistry at the Graduate School of the Mayo Foundation, "a chemist of great distinction, companion and co-worker of clinicians through many years, whose investigations of the chemistry of the thyroid gland, his isolation of crystalline glutathione, and his researches on the steroids of the adrenal gland have stimulated clinical investigation and have been of incalculable benefit to mankind."

The James D. Bruce Memorial Award was conferred upon Dr. Karl F. Meyer, Professor of Research Medicine at the University of California, Director of the Hooper Foundation for Research Medicine, "bacteriologist, protozoologist and pathologist, a persuasive teacher, a brilliant lecturer, a tireless investigator, a leader of men, whose activities have encompassed the field of preventive medicine and have led to fundamental contributions on such diverse conditions as sylvatic plague, botulism and other forms of food poisoning, undulant fever, psittacosis, leptospirosis and cutaneous hypersensitivity."

The Alfred Stengel Memorial Award was conferred upon Dr. James E. Paullin, M.A.C.P., Professor of Clinical Medicine, Emory University School of Medicine, "whose medical life has been marked by valuable contributions in the fields of pathology, clinical medicine and medical education, who has been honored by the Presidency of the American Medical Association and who has served the Armed Forces of the United States with distinction in two Wars, who became a Fellow of this College in 1928 and a Master in 1947, and who for many years as a Regent gave freely of his time and strength on important Committees. As President in wartime, between 1942 and 1944, he guided the College through a difficult period. Devotion to the aims and ideals of the College and wisdom in its councils have distinguished his career of service."

Research Fellowships for 1950-1951 were awarded to the following physicians, in accordance with one of the objects of this College to promote and advance clinical research.

- Dr. E. Harvey Estes, Jr., a graduate of Emory University School of Medicine in 1947, and designated as the Alfred Stengel Research Fellow of this College.
Dr. Dalton Jenkins, a graduate of the University of Colorado School of Medicine in 1943.
Dr. Edward H. Lanphier, a graduate of the University of Illinois College of Medicine in 1949.
Dr. William A. MacIlwaine, a graduate of the University of Virginia Department of Medicine in 1947.
Dr. Cheves McC. Smythe, a graduate of Harvard Medical School in 1947.
Dr. W. Jape Taylor, a graduate of Harvard Medical School in 1947.

In connection with the Latin-American Fellowship Program, conducted by the College in collaboration with the W. K. Kellogg Foundation, fellowships were also awarded to the following:

- Dr. Henrique Benaim Pinto, Assistant Professor of Clinical Medicine, Central University Faculty of Medicine, Caracas, Venezuela.
Dr. Fructuoso Biel Cascante, Medical Assistant in the Clinical Hospital and the University of Concepcion, Concepcion, Chile.
Dr. Rodolfo De Castro Curti, of the National University of Mexico Faculty of Medicine, Mexico, D. F.
Dr. Horacio Jinich Brook, of the National University of Mexico Faculty of Medicine, Mexico, D. F.
Dr. Francisco Lichtenberg Schneider, Ordinary Professor of Pathology, National University of Mexico Faculty of Medicine, Mexico, D. F.
Dr. Egon Lichtenberger Salomon, of the National University of Colombia Medical College, Bogota, Colombia.
Dr. Roberto Figueira Santos, of the University of Bahia Faculty of Medicine, Salvador, Brazil.

Additionally, in connection with a modified fellowship program conducted by the College and the Kellogg Foundation, a fellowship was awarded to

- Dr. Jacques Tremblay, of the University of Montreal Faculty of Medicine, Montreal, Quebec.

ELECTIONS TO MEMBERSHIP, AMERICAN COLLEGE OF PHYSICIANS

Boston, April 16, 1950

FELLOWS, FULL CAPITALS; Associates, Lower Case

- Edward William Abrams, Spokane, Wash.
MARK AISNER, Boston, Mass.
STEWART FRANCIS ALEXANDER, Park Ridge, N. J.
Max Scott Allen, Kansas City, Kans.
BARNETT ALPERT, Brooklyn, N. Y.
Michael Aronovitch, Montreal, Que., Can.
H(ARRY) THOMPSON AVEY, JR., Oklahoma City, Okla.

- Edward Bader, New York, N. Y.
HENRY JACOB BAKST, Boston, Mass.

- JAMES HENRY BARNARD, New York, N. Y.
 WILLIAM EDWIN BARNETT, Dallas, Tex.
 ALLAN DELMAGE BASS, SR., Syracuse, N. Y.
 JOHN DILLARD BATTLE, JR., Cleveland, Ohio
 Franz Karl Bauer, Los Angeles, Calif.
 THEODORE JAMES BAUER, U. S. Public Health Service
 THEODORE BEVIER BAYLES, Brookline, Mass.
 Lindsay Eugene Beaton, Tucson, Ariz.
 Hyman Belsky, Mount Vernon, N. Y.
 Richard Carlton Bennetts, Montreal, Que., Can.
 MAXWELL GLEN BERRY, Kansas City, Mo.
 Roy Stinson Bigham, Jr., Charlotte, N. C.
 Robert Allen Biles, St. Petersburg, Fla.
 WILLIAM KIRKMAN BILLINGSLEY, JR., Washington, D. C.
 James Baldwin Bingham, Jr., Seattle, Wash.
 *EDWARD FRANKLIN BLAND, Boston, Mass.
 Oscar Edgeworth Bloch, Jr., Louisville, Ky.
 William Bloom, New York, N. Y.
 RICHARD ADOLPH BLOOMFIELD, Boston, Mass.
 ROBERT ESTES BLOUNT, M.C., U. S. Army
 Samuel Mitchell Bluefarb, Chicago, Ill.
 Raymond Jerome Boller, New York, N. Y.
 Ralph Bookman, Los Angeles, Calif.
 Craig Warren Borden, Minneapolis, Minn. (V.A.)
 PAUL KENNETH BORNSTEIN, Asbury Park, N. J.
 Wade Hampton Boswell, M.C., U. S. Navy
 Harold William Bottomley, Winnipeg, Man., Can.
 Neville Clayton Bowers, M.C., U. S. Navy
 William F. Bradley, Columbus, Ohio
 Joel Jerome Brenner, New York, N. Y.
 Marion Porter Brolsma, Lincoln, Nebr.
 CARLTON F. BROWN, Detroit, Mich.
 JOHN WELCH BROWN, Madison, Wis.
 HARVEY CHRISTIAN BROWNLEY, Lynchburg, Va.
 Daniel Houston Buchanan, Jr., Denver, Colo.
 VICTOR BERNARD BUHLER, Kansas City, Mo.
 L(ester) James Buis, Richmond, Va.
 *JOSEPH JAY BUNIM, Brooklyn, N. Y.
 ALEX(ANDER) MANLIUS BURGESS, JR., Providence, R. I.
 L(OUIS) CLAIR BURKET, Altoona, Pa.
 Frank Lawrence Bynum, Fort Worth, Tex.
 JOHN WILLIAM GRANT CALDWELL, Vancouver, B. C., Can.
 Murray Hogg Campbell, Winnipeg, Man., Can.
 Harry Caplovitz, Houston, Tex.
 Richard Everett Carpenter, Oklahoma City, Okla.
 LESLIE DENIS CASSIDY, St. Louis, Mo.
 ROLANDO AUGUSTO CHANIS, Panama, R. I.
 Frederic Dunbar Chapman, Washington, D. C.
 W(ILLIAM) HOLMES CHAPMAN, JR., Suffolk, Va.
 Jules Chase, Milwaukee, Wis. (V.A.)
 *KO KUEI CHEN, Indianapolis, Ind.

* Elected to Direct Fellowship.

LOUIS CHERNIACK, Winnipeg, Man., Can.
 RUDOLPH CRESS, Topeka, Kans. (V.A.)
 HERBERT EMANUEL CHRISTMAN, Lakewood, Ohio
 Jack Sheldon Chudnoff, Los Angeles, Calif.
 JOHN JASPER CLEMMER, Albany, N. Y.
 W(ALTER) DONALD CLOSE, Indianapolis, Ind.
 Thomas Hartzelle Cobb, Pontiac, Mich.
 Jack Dexter Cohen, Brookline, Mass.
 Jules Cohen, New York, N. Y.
 Lawrence Redmond Coke, Winnipeg, Man., Can.
 Thomas Patrick Connelly, M.C., U. S. Navy
 WALTER RICHARD COOK, M.C., U. S. Army
 CRISPIN COOKE, Huntington, L. I., N. Y.
 *MAURICE JOSEPH COSTELLO, New York, N. Y.
 David Baird Coursin, Lancaster, Pa.
 GEORGE BARKSDALE CRADDOCK, Lynchburg, Va.
 Archie Crandell, Greystone Park, N. J.
 John Elwin Crary, Topeka, Kans.
 HATCH WHITFIELD CUMMINGS, JR., Houston, Tex.

Angelo Emil Dagradi, Northport, N. Y. (V.A.)
 David Alfred Dantes, Los Angeles, Calif. (V.A.)
 CHARLES SPRECHER DAVIDSON, Boston, Mass.
 Ralph Myers Denham, Detroit, Mich.
 Randall Sylvester Derifield, Des Moines, Iowa (V.A.)
 Bertram Harold Dessel, Milwaukee, Wis. (V.A.)
 John J. Donnell, Oklahoma City, Okla.
 Vincent Michael Downey, M.C., U. S. Air Force
 David Thomas Dresdale, Brooklyn, N. Y.
 MARSHALL FLETCHER DRIGGS, Englewood, N. J.
 Melville Morgan Driskell, M.C., U. S. Navy
 C(rawford) Dary Dunham, New York, N. Y.
 THELMA BRUMFIELD DUNN, Bethesda, Md.
 RALPH EVERETT DURKEE, JR., Hartford, Conn.
 Simon Dworkin, Montreal, Que., Can.

RICHARD VINCENT EBERT, Minneapolis, Minn. (V.A.)
 DONALD THOMAS EDMANDES, Pasadena, Calif.
 *LAURENCE BREWSTER ELLIS, Boston, Mass.
 Leo Elson, Jackson, Miss. (V.A.)
 Charles Darwin Enselberg, New York, N. Y.
 John Earle Estes, Rochester, Minn.
 SILAS McAFEE EVANS, Milwaukee, Wis.

Howard Douglas Fabing, Cincinnati, Ohio
 Chester Wilson Fairlie, Jr., Rocky Hill, Conn.
 WILLIAM FEIRING, Richmond Hill, N. Y.
 Joel Feldman, Red Bank, N. J.
 Theodore Feldman, Boston, Mass.
 Samuel Gustav Feuer, Brooklyn, N. Y.
 M(EYER) HERBERT FINEBERG, Dwight, Ill. (V.A.)
 Karl Fischbach, New York, N. Y.

* Elected to Direct Fellowship.

JACOB WARREN FISCHER, Chicago, Ill.
Robert Edmund Fisher, Bay City, Mich.
Seymour Fisher, Fort Benjamin Harrison, Ind. (V.A.)
DAVID MOYLE FLETT, Cheyenne, Wyo.
LLOYD JOSEPH FLORIO, Denver, Colo.
Frederick Rahde Franke, Pittsburgh, Pa.
Arthur Merrimon Freeman, Jr., Birmingham, Ala.
Harry Freund, Brooklyn, N. Y.
HARRY BERNARD FRIEDGOOD, Beverly Hills, Calif.
Jackson Harrison Friedlander, Northport, N. Y. (V.A.)
BURT FRIEDMAN, Memphis, Tenn.
Isaac Spitz Friedman, Brooklyn, N. Y.
ROBERT ABRAHAM FRISCH, Milwaukee, Wis.

JOSEPH MARTIN GANNON, Plainfield, N. J.
JOHN EDWARD GARCIA, New Orleans, La.
MAXWELL L. GELFAND, New York, N. Y.
BENJAMIN ROBERT GENDEL, Memphis, Tenn. (V.A.)
Harold N. Gilbert, Santa Monica, Calif.
FREDERICK LEMUEL GILES, Honolulu, T. H.
David John Gilmore, Salisbury, Md.
James Francis Gleason, Atlantic City, N. J.
BERNARD ISADORE GOLDBERG, Newton Center, Mass.
Hymen Maxwell Golden, Flint, Mich.
John James Goldsberry, Worcester, Mass.
Gilbert S. Gordan, Jr., San Francisco, Calif.
EDDIE MONROE GORDON, JR., U. S. Public Health Service
John Edward Gorman, M.C., U. S. Navy
ABRAHAM MITCHELL GOTTLIEB, Detroit, Mich. (V.A.)
*G. HOWARD GOWEN, Springfield, Ill.
LOUIS W. GRANIRER, Broad Channel, N. Y.
ROBERT COLEMAN GRAUER, Pittsburgh, Pa.
SEYMOUR JEROME GRAY, Boston, Mass.
*HUGH PAYNE GREELEY, Boston, Mass.
MERVIN EDWARD GREEN, Toledo, Ohio
Raphael Herman Greenstein, Philadelphia, Pa.
TIBOR JACK GREENWALT, Milwaukee, Wis.
ALTON CLAREN GRORUD, Bismarck, N. D.
Moses Gross, Brooklyn, N. Y.
George Erwin Gutman, Janesville, Wis.

PAUL OONK HAGEMANN, St. Louis, Mo.
Paul Stickney Hagen, Minneapolis, Minn. (V.A.)
David Lucian Halbersleben, Boston, Mass.
Arvel Edwin Haley, Dallas, Tex.
Wendell Howard Hall, Minneapolis, Minn. (V.A.)
Jacob Halpern, Brooklyn, N. Y.
LAWRENCE JAMES HALPIN, Cedar Rapids, Iowa
Stearley P. Harrison, Oklahoma City, Okla.
ROBERT BARRON HAVELL, Washington, D. C.
JAMES WEST HAVILAND, Seattle, Wash.
Mary Krise Helz, Pittsburgh, Pa.

* Elected to Direct Fellowship.

James Robert Hendon, Louisville, Ky.
Frank Thompson Herron, Pittsburgh, Pa.
Edward Clyde Heyde, Vancouver, Wash.
William Harrison Higgins, Jr., Richmond, Va.
IREDELL MELVIN HINNANT, Cleveland, Ohio
JOHN STEPHEN HIRSCHBOECK, Milwaukee, Wis.
HORACE HAYDEN HODGES, Charlotte, N. C.
Fredrick William Hoffbauer, St. Paul, Minn.
Jacob William Holler, Bradford, Pa.
EDWARD ESTIS HOLLOWAY, Philadelphia, Pa.
DELANVAN VAN HORN HOLMAN, New York, N. Y.
Fred Weber Holmes, Phoenix, Ariz.
ARNOLD BEVERLEY HOUSTON, Winnipeg, Man., Can.
Bernard Hyde, Los Angeles, Calif.

Nelson Sumner Irely, M.C., U. S. Army
Lawrence Neff Irvin, Lima, Ohio
HARRIS ISBELL, U. S. Public Health Service
EMIL MARK ISBERG, Miami Beach, Fla.

LEIF YNGVE JACOBSEN, Douglaston, L. I., N. Y.
LEON ORRIS JACOBSON, Chicago, Ill.
WILLIAM ALLEN JEFFERS, Philadelphia, Pa.
BENJAMIN JEFFRIES, Detroit, Mich.
Richard Jessup, Meadville, Pa.
Frank Donald Johnson, Flint, Mich.
Elmer Knox Jones, Wellington, Tex.
NATHANIEL JONES, SR., Jacksonville, Fla.

JERALD SCOTT KALTER, New York, N. Y.
GEORGE KAPLAN, Palm Springs, Calif.
LOUIS A. KAPP, White Plains, N. Y. (V.A.)
ABRAHAM JUDAH KAUVAR, Denver, Colo.
Philip Gerald Keil, Des Moines, Iowa (V.A.)
MAVIS PARROTT KELSEY, Houston, Tex.
RICHARD JOSEPH KENNEDY, New York, N. Y.
Thomas Jackson Kenyon, St. Paul, Minn.
DOROTHEA MARIA KILLIAN, Philadelphia, Pa.
Jack Murry Klufft, Perth Amboy, N. J.
William Allen Knight, Jr., St. Louis, Mo.
Roland Ferguson Knox, Wichita Falls, Tex.
JACOB JOHN KOHLHAS, Haverford, Pa.
OTTO ALBIN KOSTAL, Hastings, Nebr.
PAUL KUNKEL, Newington, Conn. (V.A.)
Edgar Ross Kyger, Jr., Fort Worth, Tex.

ALFRED CHARLES LaBOCCETTA, Philadelphia, Pa.
William Joseph Lahey, Hartford, Conn. (V.A.)
PAUL HARRY LANGNER, JR., Drexel Hill, Pa.
Reuben T. Lapidus, Poughkeepsie, N. Y.
Homer Edson Lawrence, Concord, N. H.
James Wilson Leatherman, Hot Springs National Park, Ark.
William Louis Lehman, Portland, Ore.

GEORGE CHARLES LEINER, New York, N. Y.
Frank Leone, Kew Gardens, N. Y.
Howard Levine, New Britain, Conn.
JOHN ALBERT LEWIS, London, Ont., Can.
MERLYN CARL FRED LINDERT, Milwaukee, Wis.
Leonard Sandford Linkner, Detroit, Mich.
DAVID ERNEST LISTON, M.C., U. S. Army
Wallace H. Livingston, Jr., Denver, Colo.
Albert Marsee Lupton, Philadelphia, Pa.
Victor Ivan Lyday, Dallas, Tex.
GEORGE WILLIAM LYNCH, Boston, Mass.
HAROLD ALOYSIUS LYONS, M.C., U. S. Navy

John Burton MacGregor, M.C., U. S. Navy
GULDEN MACKMULL, Philadelphia, Pa.
A(LEC) CAMERON MacNIEL, Shaker Heights, Ohio
Elliott Francis Maguire, Philadelphia, Pa.
DONALD LUTHER MAHANNA, Columbus, Ohio
Emanuel Emil Mandel, U. S. Public Health Service
FRANCIS ROXBOROUGH MANLOVE, Philadelphia, Pa.
Albert William Mann, Santa Monica, Calif.
Wilbur Berry Manter, Bangor, Maine
CASPER MARKEL, Denver, Colo.
Arne Kristian Mathisen, Vancouver, B. C., Can.
Harry Brendan McCluskey, East Orange, N. J.
FLORENCE SPAULDING McCONNEY, Toronto, Ont., Can.
James Edward McCormack, New York, N. Y.
Richard Ronald Cormac McCormack, New York, N. Y.
Ronald Hugh McFarlane, Winnipeg, Man., Can.
James Edward McGinnis, Los Angeles, Calif.
Thomas Aloysius McGoldrick, Jr., Savannah, Ga.
John Gilmer Mebane, Rutherfordton, N. C.
WALLACE ALFRED MERRITT, Rochester, Minn.
Luigi Pietro Minetto, Brooklyn, N. Y.
Dana Covington Mitchell, Jr., Columbia, S. C.
Robert Carl Mitterling, Springfield, Pa.
Arnold Sofus Moe, East St. Louis, Ill.
George Edmond Montgomery, Jr., Ames, Iowa
MATTHEW THIBAUD MOORE, Philadelphia, Pa.
William Hopkins Moorhead, Houston, Tex.
John Lloyd Morgan, Emporia, Kans.
FRED HOWENSTINE MOWREY, M.C., U. S. Army
Robert Kerwin Moxon, M.C., U. S. Navy
George William Murgatroyd, Jr., Baltimore, Md.
JAMES PATRICK MURPHY, St. Louis, Mo.
Francis James Murray, Washington, D.C.
Ralph Mayer Myerson, Wilmington, Del. (V.A.)
*LOUIS NATHANSON, Brooklyn, N. Y.
LOUIS GEORGE NEUDORFF, St. Joseph, Mo.
Otto Neurath, Beverly Hills, Calif.
Glenn Carraway Newman, Clinton, N. C.
Donald Richardson Nichols, Rochester, Minn.

* Elected to Direct Fellowship.

EDWARD NICHOLS, Hartford, Conn.

*JOHN WILLIAM ROY NORTON, Raleigh, N. C.
Harry Nushan, Kecoughtan, Va. (V.A.)

SIDNEY G. ODLE, Pittsburgh, Pa.

BENJAMIN GERSHWIN OREN, Miami, Fla.

DAVID HAROLD PALEY, New York, N. Y.

*JOHN HAMMOND PALMER, Montreal, Que., Can.

Joseph Freeman Paquet, Portland, Ore.

GEORGE MASON PARKER, Peoria, Ill.

Alfred Edward Passera, Woodside, N. Y.

Thomas Earl Patton, Jr., M.C., U. S. Army

James Donald Peirce, Jr., Indianapolis, Ind.

Alfred William Pennington, Wilmington, Del.

Anthony Felix Perl, Sarnia, Ont., Can.

CORNELIUS C. PERRINE, Fair Haven, N. J.

Louis Yale Peskoe, Augusta, Ga. (V.A.)

BRUNO JOSEPH PETERS, Milwaukee, Wis.

CLIFFORD HENRY PETERS, Bismarck, N. D.

Donald Bullen Peterson, M.C., U. S. Army

Karl M. Pickard, Brooklyn, N. Y.

ARNOLD WAITE POHL, Albany, N. Y.

Phillip Polatin, New York, N. Y.

Max Pomerance, Brooklyn, N. Y.

Clement Bartholomew Potelunas, Wilkes-Barre, Pa.

David William Quick, Jr., Beaumont, Tex.

Leon Lionel Rackow, Tuscaloosa, Ala. (V.A.)

Frederick Ferdinand Radloff, Wenatchee, Wash.

EDWARD COWELL RAFFENSPERGER, Harrisburg, Pa.

Oscar Benjamin Ragins, Chicago, Ill.

JOSEPH WALTER RASTETTER, Milwaukee, Wis.

C(larence) Thorpe Ray, New Orleans, La.

PHILIP BYRON REED, Indianapolis, Ind.

William Henry Reiff, Oklahoma City, Okla.

WILLIAM ANTON HENRY RETTBERG, Denver, Colo.

FRANK WALKER REYNOLDS, Geneva, Switzerland

NORMAN BRIDGE ROBERG, Chicago, Ill.

C(HARLES) PURCELL ROBERTS, Atlanta, Ga.

ARTHUR BENJAMIN ROBINS, New York, N. Y.

JOSE GAMMA RODARTE, Temple, Tex.

ANGEL RODRIGUEZ-OLLEROS, San Juan, P. R.

JOHN DAVID ROGER, Ottawa, Ont., Can.

John A. Roque, Cranston, R. I.

NATHANIEL EDWARD ROSSETT, Memphis, Tenn. (V.A.)

NORMAN OLIVER ROTHERMICH, Columbus, Ohio

Leo Rubenstein, New York, N. Y.

Herman Rudensky, Fort Benjamin Harrison, Ind. (V.A.)

Jack Arthur Rudolph, Miami Beach, Fla. (V.A.)

MILTON JEROME RUEGER, Grosse Pointe Farms, Mich.

* Elected to Direct Fellowship.

CARLOS FRANCISCO SACASA, Pasadena, Calif.
BYRON DOUGLAS SAINT JOHN, Port Washington, N. Y.
PIERRE SALMON, Brooklyn, N. Y.
ALEXANDER SANDERS, Chicago, Ill.
ALBERT CHRISTY SANTY, New York, N. Y.
SANFORD SARNEY, Brooklyn, N. Y.
Joseph Edwin Schenthal, New Orleans, La.
C(LARENCE) BENJAMIN SCHOEMPERLEN, Winnipeg, Man., Can.
EMANUEL BARNETT SCHOENBACH, Baltimore, Md.
Robert Henry Schoene, Columbus, Ohio
J(ACK) SPALDING SCHRODER, Emory University, Ga.
DAVID SCHWIMMER, New York, N. Y.
Vincent Felix Sciuillo, Baltimore, Md. (V.A.)
Stewart Pinnell Seigle, Hartford, Conn.
LAURENCE A. SENSEMAN, Saylesville, R. I.
Irving Chanin Shavelson, Atlantic City, N. J.
Harman Albert Shecket, Cleveland, Ohio
Walter Brown Shelley, Hanover, N. H.
Jack Courtney Shrader, Pasadena, Calif.
SHEPPARD SIEGAL, New York, N. Y.
LEON SAMUEL SMELO, Birmingham, Ala.
Alfred Littlefield Smith, Richmond, Va.
ARTHUR LAWRENCE SMITH, JR., Lincoln, Nebr.
Durwood James Smith, Rochester, N. Y.
JASPER ARCHER SMITH, Waterbury, Conn.
Merl Bernard Smith, Toledo, Ohio
SOL(OMON) SMITH, Baltimore, Md.
SYDNEY SOLOMON, Stamford, N. Y.
S(AMSON) ZELIG SORKIN, New York, N. Y.
HAMILTON SOUTHWORTH, New York, N. Y.
Bertram Edward Sprofskin, Nashville, Tenn.
David Steinberg, Jamaica, N. Y.
Robert Alexander Steven, San Francisco, Calif.
ROBERT EDWARDS STONE, Birmingham, Ala.
S(AMUEL) FREDERICK STRAIN, Memphis, Tenn.
* ARTHUR EDGAR STRAUSS, St. Louis, Mo.
Clyde Scott Stroud, Jr., M.C., U. S. Navy
Clayton King Stroup, Flint, Mich.
MARCUS HOWARD SUGARMAN, Detroit, Mich.
James Polk Sullivan, M.C., U. S. Army
DANIEL MASON SWAN, Quincy, Mass.
MERLE HARRIS SWANSEN, Klamath Falls, Ore.

ERNEST MARVIN TAPP, Grand Junction, Colo. (V.A.)
LEONARD TARR, New York, N. Y.
HUGH TATLOCK, Northampton, Mass.
MEYER TEXON, New York, N. Y.
JAMES HARWOOD THOMPSON, San Francisco, Calif.
WILLIAM ALBERT THORNHILL, JR., Charleston, W. Va.
LESLIE MELVIN TOWNSEND, Roselle Park, N. J.
JOHN DAVID TRAWICK, JR., Louisville, Ky.
H(ENRY) ST. GEORGE TUCKER, JR., Richmond, Va.

* Elected to Direct Fellowship.

Maurice Tulin, New York, N. Y.
James Baker Twyman, Charlottesville, Va.

Lee Chester Underwood, Jr., Canton, Ohio
DAN LOWELL URSCHER, Mentone, Ind.

ALBERT VanderKLOOT, Chicago, Ill.
W(ILLIAM) ALFRED VAN ORMER, Cumberland, Md.
KARL OTTO Von HAGEN, Los Angeles, Calif.

RICHARD CLARKE WADSWORTH, Bangor, Maine
IRVING MANFORD WAGGONER, West Chester, Pa.
Benjamin Cicero Wallace, Jr., Waxahachie, Tex.
Israel Walzer, Whipple, Ariz. (V.A.)
THOMAS ANGELL WARTHIN, Natick, Mass. (V.A.)
MYRON McDONALD WEAVER, Vancouver, B. C., Can.
RICHARD FOUKE WEBB, Pasadena, Calif.
William Morrow Webb, M.C., U. S. Army
HYAM ARNE WEINER, Staten Island, N. Y. (V.A.)
JOSEPH G. WEINER, Philadelphia, Pa.
Henry Joseph Weintraub, New York, N. Y.
Jonas Weissberg, Elizabeth, N. J.
JACK WEXLER, Baltimore, Md.
ROBERT LaFAYETTE WHIPPLE, JR., Atlanta, Ga.
D(ennis) Naldrett White, Kingston, Ont., Can.
Robert Morris White, New Haven, Conn.
Bert(ram) Hirsh Wiesel, Birmingham, Ala.
Armistead Dandridge Williams, Richmond, Va.
John Henry Wishart, Eau Claire, Wis.
Richard H. Wright, Brookline, Mass.
Otto Albert Wurl, M.C., U. S. Army

SAMUEL ZELMAN, Topeka, Kans. (V.A.)
Gary Zucker, New York, N. Y.

A.C.P. POSTGRADUATE COURSES

At the publication of this notice all courses on the Spring 1950 schedule of the College will have been concluded with the exception of Course No. 9, CLINICAL ASPECTS OF MALNUTRITION, August 14-26, 1950, at the Hospital de Enfermedades de la Nutricion, Mexico, D. F., under the directorship of Salvador Zubiran, M.D., F.A.C.P. The full outline and other details concerning this course were published in the April 1950 issue of this journal. This two-weeks course as organized will be one of the most informative, basically sound and practical courses in this field ever offered. Nevertheless, adequate interest in registering for the course has not yet developed. The number registered is comparatively small and the College cannot impose upon the time of the faculty in Mexico unless a more representative registration develops at once.

Autumn 1950 Schedule

The following courses will be given under the auspices of the American College of Physicians during the autumn of 1950. The postgraduate bulletin will be published during July and distributed to all members and to those non-members who have requested that their names be placed on the mailing list.

INTERNAL MEDICINE: SELECTED SUBJECTS, University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director; one week, September 25-30.

PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE, Duke University School of Medicine, Durham, N. C.; Eugene A. Stead, M.D., F.A.C.P., Director; one week, October 9-14.

CRITICAL PROBLEMS IN INTERNAL MEDICINE, University of Chicago School of Medicine, Chicago, Ill.; Wright Adams, M.D., F.A.C.P., Director; one week, October 23-27.

CLINICAL ALLERGY, Institute of Allergy, Roosevelt Hospital, New York, N. Y.; Robert A. Cooke, M.D., F.A.C.P., Director; two weeks, October 23-November 4.

RECENT DEVELOPMENTS IN MEDICINE, University of Utah College of Medicine, Salt Lake City, Utah; Max M. Wintrobe, M.D., F.A.C.P., Director; one week, November 6-11.

GASTRO-ENTEROLOGY, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director; one week, December 4-9.

PERIPHERAL VASCULAR DISEASES INCLUDING HYPERTENSION, Mayo Clinic and Mayo Foundation, Rochester, Minn.; Walter F. Kvale, M.D., F.A.C.P., Director; E. V. Allen, M.D., F.A.C.P., Nelson W. Barker, M.D., F.A.C.P., John E. Estes, M.D., (Associate), Edgar A. Hines, Jr., M.D., F.A.C.P., and Richard M. Shick, M.D., F.A.C.P., Co-Directors; one week, December 4-9.

HEMATOLOGY, New England Medical Center, Boston, Mass.; William Dameshek, M.D., F.A.C.P., Director; one week, December 11-16.

NEW LIFE MEMBERS

The College is gratified to announce that the following Fellows, in order listed, have become Life Members of the American College of Physicians since the publication of the latest issue of this journal:

Forrest Nelson Anderson, Van Nuys, Calif.
Robert M. Hoyne, Urbana, Ill.
Sidney L. Penner, Stratford, Conn.
Louis Nathanson, Brooklyn, N. Y.

The College has an equitable and practicable Life Membership plan whereby members may underwrite their future dues during their productive years, while income is greatest. Life Membership offers security in advancing years against misfortunes which often necessitate the relinquishment of one's most cherished professional memberships because of the burden of dues. All Life Membership fees are added to the permanent Endowment Fund of the College, and thus contribute to the security of the College as well as to the security of its members. The Life Membership fee is deductible on Federal income tax returns, thus offering very substantial savings to the subscriber.

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made to Dr. Paul R. Hawley, F.A.C.P., Chicago, Ill., for an autographed copy of his book, "New Discoveries in Medicine, Their Effect on the Public Health." This book comprises the Bampton Lectures, second series, and has just been published by the Columbia University Press.

The College library is also indebted to Dr. H. Sheridan Baketel, F.A.C.P., Chairman of the Reed & Carnrick Institute for Medical Research, for two books over four hundred years old. One is "Methodus Medicamenta Componendi," published in Paris in 1541 in Latin; the other, "Galenī Pergameni," published in Basileae in 1538. The latter book is printed partially in Latin, with the main text in Greek. Both of these books are in an excellent state of preservation.

AMERICAN BOARD OF INTERNAL MEDICINE

The following physicians comprise the American Board of Internal Medicine:

Truman G. Schnabel, Philadelphia (A.C.P.), Chairman
M. A. Blankenhorn, Cincinnati (A.M.A.)
LeRoy H. Briggs, San Francisco (A.M.A.)
Alex. M. Burgess, Providence (A.C.P.)
Chester M. Jones, Boston (A.C.P.)
Walter L. Palmer, Chicago (A.C.P.)
William B. Porter, Richmond (A.C.P.)
Burrell O. Raulston, Los Angeles (A.M.A.)
Roy W. Scott, Cleveland (A.C.P.)
Albert M. Snell, Rochester, Minn. (A.C.P.)
Virgil P. Sydenstricker, Augusta (A.M.A.)
Henry M. Thomas, Jr., Baltimore (A.M.A.)

All official correspondence and requests for application forms should be addressed to: William A. Werrell, M.D., Assistant Secretary-Treasurer, 1 West Main St., Madison 3, Wis.

POSTGRADUATE COURSE, DIAGNOSIS AND THERAPY OF CANCER

The University Extension of the University of California has announced a post-graduate course in "Diagnosis and Therapy of Cancer" to be given at the Medical Library Conference Room of the General Medical and Surgical Hospital, Veterans Administration Center, Los Angeles, from July 17-22, 1950. The course is open only to graduates of approved medical schools, and the fee is \$100.00. Detailed outline of the course and personnel of the faculty may be obtained from the Office of Medical Extension, University of California, Los Angeles 24, Calif.

The Los Angeles Heart Association is offering an award of \$100.00 for a paper of merit on any subject of current interest in the general field of cardio-vascular disease. The winner of the award will have the opportunity to present the paper at the Fall Symposium of the Association. Anyone now serving as either an interne or a resident at any approved hospital in Southern California may submit an entry. Also, anyone who has completed an internship or a residency at any Southern California hospital within the past twelve months shall be eligible to enter the contest provided the paper is based on observations or study done during his hospital period. Papers must be in the hands of the secretary not later than August 1, 1950. All com-

munications should be addressed to the Los Angeles Heart Association, c/o Dr. William D. Evans, F.A.C.P., Secretary, 1670 Beverly Blv., Los Angeles 26, Calif.

The International Congress of Internal Medicine will be held in Paris, France, September 11-14. Among the speakers on the program are Dr. Byron E. Hall, F.A.C.P., Rochester, Minn.; Dr. George W. Thorn, F.A.C.P., Boston, Mass.; and Dr. William J. Kerr, F.A.C.P., San Francisco, Calif.

UNITED STATES PHARMACOPOEIAL CONVENTION

Decennial Period, 1940-1950

The Decennial Meeting of the United States Pharmacopoeial Convention was held at Washington, D. C., May 9-10, 1950, under the Presidency of Cary Eggleston, M.D. The official delegates of the American College of Physicians included Walter W. Palmer, M.D., F.A.C.P., New York City; Chester S. Keefer, M.D., F.A.C.P., Boston; and Marion A. Blankenhorn, M.D., F.A.C.P., Cincinnati.

The annual meeting of the American Therapeutic Society was held in Boston, Mass., April 13-16, under the Presidency of Dr. Daniel L. Sexton, F.A.C.P., St. Louis, Mo. Among those taking part in a symposium on ACTH were Dr. Willard O. Thompson, F.A.C.P., Chicago, Ill.; Dr. George W. Thorn, F.A.C.P., Boston, Mass.; Dr. W. Paul Holbrook, F.A.C.P., Tucson, Ariz.; and Dr. Francis M. Pottinger, Jr., F.A.C.P., Monrovia, Calif.

The American Gastroenterological Association held its annual meeting in Atlantic City, N. J., April 28-29, under the Presidency of Dr. J. Arnold Barger, F.A.C.P., Rochester, Minn. Dr. B. B. Vincent Lyon, F.A.C.P., Philadelphia, Pa., was presented the Julius Friedenwald Medal at the annual dinner.

The Henry B. Shmookler Memorial Lecture was delivered by Dr. Maxwell M. Wintrobe, F.A.C.P., Salt Lake City, Utah, at the Mt. Sinai Hospital, Philadelphia, Pa., on May 3. Dr. Wintrobe's subject was "Management of Hodgkin's Disease, the Leukemias and Related Disorders."

The annual John Wyckoff Lecture was delivered at New York University College of Medicine by Dr. George W. Thorn, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, Boston, Mass. Dr. Thorn spoke on "Studies on the Use of ACTH and Cortisone" on March 28, and "Clinical Use of the Artificial Kidney" on March 29.

Dr. Albert M. Snell, F.A.C.P., formerly Professor of Medicine at the Mayo Foundation Graduate School, Rochester, Minn., was appointed Director of Clinical Studies at the Palo Alto Medical Research Foundation, which opened on April 1. The Foundation will offer research facilities and trained research assistance to physicians in private practice.

Dr. Leon L. Gardner, F.A.C.P. (Col. M.C., U.S.A., Retired), has been appointed Chief of Preventive Medicine of the City of Richmond, Va., and will also serve as Associate Professor of Preventive Medicine at the Medical College of Virginia.

Dr. Cyrus C. Sturgis, F.A.C.P., Professor of Medicine, University of Michigan Medical School, delivered the ninth Edwin R. Kretschmer Memorial Lecture of the Institute of Medicine of Chicago on April 28. His subject was "An Evaluation of the Nature, Treatment and Prognosis of Leukemia."

The President of the Dominican Republic, Generalissimo Rafael Molina Trujillo, has recently conferred on Dr. J. C. Geiger, F.A.C.P., Director of Public Health, San Francisco, the additional grade of Grand Officer, with star or plaque of the Order of Honor and Merit of Juan Pablo Duarte. Dr. Geiger's citation stated that this honor was "For distinguished service in the public health in Latin American Countries and particularly to the Dominican Republic." This decoration was first bestowed on Dr. Geiger in 1945 in the grade of Commander.

At its annual meeting in Atlantic City on April 19, the American Institute of Nutrition presented the Meade Johnson Vitamin B-Complex Award to Dr. William B. Castle, F.A.C.P., Boston, Mass., "in recognition of his classic investigations leading to the concept of intrinsic and extrinsic factors in pernicious anemia, and of his studies elucidating the relation of vitamin B12 to this concept."

Dr. Harry F. Dowling, F.A.C.P., Washington, D. C., has been named Professor and Head of the newly established Department of Preventive Medicine at the University of Illinois College of Medicine.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., was tendered a testimonial dinner at Asbury Park, N. J., on June 11, 1950, by the New Jersey Gastroenterological Society, which is a Chapter of the National Gastroenterological Association.

At the annual meeting of the National Tuberculosis Association held in Washington, D. C., April 24-28, Dr. Leonard A. Scheele, F.A.C.P., Washington, D. C., was elected honorary Vice President, and Dr. Frank L. Jennings, F.A.C.P., Indianapolis, Ind.; Dr. Rollin D. Thompson, F.A.C.P., West Palm Beach, Fla.; and Dr. Sidney J. Shipman, F.A.C.P., San Francisco, Calif., were elected to the Executive Committee. Among the newly elected members of the Board of Directors are Dr. William D. Province (Associate), Franklin, Ind.; Dr. Arthur A. Herold, F.A.C.P., Shreveport, La.; and Dr. Robert G. Bloch, F.A.C.P., Chicago, Ill. Dr. John H. Skavlem, F.A.C.P., Cincinnati, Ohio, was elected President-Elect of the American Trudeau Society.

Dr. John Z. Bowers (Associate), Baltimore, Md., has been appointed Dean of the University of Utah College of Medicine, Salt Lake City. He will succeed Dr. Richard H. Young, F.A.C.P., who became Dean of Northwestern University School of Medicine, Chicago, Ill.

At the annual Alumni Day exercises of the Cornell University Medical College, held March 23, 1950, the second Annual Award for distinguished service to medicine was presented to Dr. David P. Barr, F.A.C.P., Professor of Medicine at Cornell, and past President of the American College of Physicians.

Dr. Virgil P. Sydenstricker, M.A.C.P., and Dr. Edgar R. Pund, F.A.C.P., both of Augusta, Ga., have been commended by Major General Raymond W. Bliss, F.A.C.P., Surgeon General, U. S. Army, for their outstanding contributions to the Army Graduate Professional Training Program.

At the annual meeting of the Hawaii Territorial Medical Association held on May 4-7 in Hilo, Dr. Paul D. White, F.A.C.P., Boston, Mass., spoke on "Heart Disease in Middle Age." Dr. White will later conduct a two week series of post-graduate lectures in Honolulu and will also address the Kauai and Maui counties medical societies.

Friends and former students of Dr. Archibald L. Hoyne, F.A.C.P., Chicago, Ill., honored him with a dinner on June 1. The occasion marked the retirement of Dr. Hoyne after serving thirty years as Medical Superintendent of the Chicago Municipal Contagious Disease Hospital.

Dr. Philip S. Hench, F.A.C.P., and Edward C. Kendall, Sc.D., both of the Mayo Clinic, Rochester, Minn., will be honored with a \$5,000 cash award by the Passano Foundation for their studies in clinical physiology as related to the administration of cortisone and related hormones. The award will be presented at the annual award dinner to be held in San Francisco on June 28.

On April 14 Dr. Hench and Dr. Kendall received bronze replicas of a printer's composing stick from the New York City chapter of the American Newspaper Guild. This award was one of eleven conferred on persons in special fields for their "contributions to social or cultural progress."

Brigadier General Arthur R. Gaines, M.C., U.S.A., F.A.C.P., Commanding Officer of Brooke General Hospital, Fort San Houston, Texas, has been nominated by President Truman for promotion to the rank of Major General.

Dr. William F. Ashe, F.A.C.P., Associate Professor of Industrial Medicine at the University of Cincinnati College of Medicine, has resigned to become Chief of the Medical Service of the Holzer Clinic and Director of the Department of Internal Medicine of the Holzer Hospital in Gallipolis, Ohio.

At a joint meeting with the Laennec Society of Philadelphia, the Philadelphia County Medical Society awarded to Dr. Esmond R. Long, F.A.C.P., the twenty-sixth annual Strittmatter gold medal and scroll on April 12.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., has been appointed Medical Editor of "GP," published by the American Academy of General Practice. Dr. Alvarez is retiring from the Mayo Clinic where he has been associated since 1926, and will move to Chicago to assume his new duties.

Dr. John G. Mateer, F.A.C.P., Detroit, and Dr. T. Grier Miller, F.A.C.P., Philadelphia, were elected President and First Vice President, respectively, by the American Gastroenterological Association at its recent meeting at Atlantic City.

MEDICAL ILLUSTRATORS' DIRECTORY AVAILABLE

The Directory issue of GRAPHICS, the official publication of the Association of Medical Illustrators, contains the name, address, training, professional experience and reference to major published work of each member. Other information pertaining to the profession is included.

The journal, issued on June 1, is available to those requiring medical illustration service, and will be sent free of charge, upon request to the Editor, Miss Helen Lorraine, 5212 Sylvan Road, Richmond 25, Va.

MEDICAL TEACHING MOTION PICTURES NOW IN PRODUCTION

The Medical Film Institute of the Association of American Medical Colleges, 2 East 103rd Street, New York 29, N. Y., has issued a catalog of medical teaching motion pictures now in process of production or already completed. The films are in the fields of anatomy, bacteriology—parasitology—basic biology, dermatology, eye-ear-nose and throat, gynecology, internal medicine, neurology, obstetrics, orthopedic surgery, pathology, pediatrics, physical medicine, physiology, preventive medicine—public health, radiology, surgery and urology. The catalog, prepared in a convenient manner for displaying on bulletin boards, gives the title of each motion picture, its specifications as to millimeter, color, sound, sponsorship and scientific adviser, a brief description of the film and advice as to the audience for which the film was prepared.

NATIONAL SCIENCE FOUNDATION BILL PASSES

The National Science Foundation Bill has been passed and a 24-member Board that will govern the Foundation is being formed. Legislation directs that the President shall give due consideration to recommendations for Board membership according to nominations submitted by various scientific and educational organizations, including the National Academy of Sciences; the Association of Land Grant Colleges and Universities, the Association of American Colleges and the National Association of State Universities. With the advice and consent of the Senate, President Truman is empowered to appoint a Director of the Foundation. However, the Director is not to be appointed until the Board has been formed and has had an opportunity to submit its recommendations. The post will pay a salary of \$15,000 per annum. The term of office will be six years. It is still required that Congress pass the necessary appropriation bill for the operation of the Foundation.

ARMY MEDICAL LIBRARY CATALOG CARDS

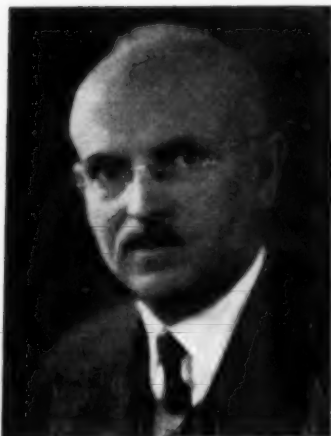
An announcement in the March 1950 issue of the *Army Medical News* letter, the Card Division of the Library of Congress will duplicate (by the multilith process) and sell single copies of catalog cards on a subscription basis of \$100.00 per year. Card shipments will be made every two weeks.

These cards represent medical titles (for which there are no Library of Congress printed cards) cataloged or recataloged by the Army Medical Library and will total approximately 10,000 for the year of 1950 beginning January 1.

Orders may be addressed to the Card Division, Library of Congress, Washington 25, D. C.

OBITUARIES

DR. G. GILL RICHARDS



G. Gill Richards, M.D., F.A.C.P., Salt Lake City, Utah, died while in attendance at the 31st Annual Session of the American College of Physicians at Boston, April 20, 1950, of a heart attack.

Dr. Richards was born in Mendon, Utah, September 5, 1883. He attended the Salt Lake City Public Schools and spent two years at the University of Utah in the Academic Department. He entered University and Bellevue Medical College, New York City, in 1902, transferred one year, 1903, to Rush Medical College, Chicago, and then returned to New York, receiving his M.D. from the University and Bellevue Hospital Medical College in 1906. After graduation he returned to Salt Lake City to enter practice with his father. In 1910, and in 1912, he did post-graduate work in Vienna and Berlin.

He was one of the founders of the Salt Lake Clinic and served as head of the Department of Medicine since the clinic was founded in 1915. He was a Member of the Staff of the Dr. W. H. Groves Latter-Day Saints Hospital for over forty years.

He was Clinical Professor of Medicine, University of Utah College of Medicine, and contributed much to the progress of the medical school. He was a member of the Dean's Committee of the Veterans Administration Hospital.

Dr. Richards was a charter Diplomate of the American Board of Internal Medicine, and for twelve years was a member of that Board. He was a Fellow of the American College of Physicians since 1920; Governor of the College for Utah from 1926-1934; Regent from 1934-1937; Second Vice President, 1937-1938; and served on numerous committees of the College. He was a member of the Pacific Interurban Clinical Club, and was at one time Chairman of the section in Internal Medicine of the American Medical Association.

Dr. Richards was the author of numerous articles published in leading medical journals throughout the years.

In November, 1949, he received the University of California Medical School's Gold Headed Cane award as an outstanding physician.

On September 3, 1912, Dr. Richards married Florence Lott Farnsworth. She died in June, 1933, and in March, 1938, he married Lacy Jane Farnsworth who survives him. He was an active member of the Church of Jesus Christ of Latter-Day Saints. Surviving him, in addition to his widow, are a son and daughter, Dr. Harlow Gill Richards, Salt Lake City, Mrs. Kenneth L. Burton of Ogden, three grandchildren, four brothers, and a sister.

FULLER B. BAILEY, M.D., F.A.C.P.,

Governor for Utah

DR. WILLIAM BOYD READING

Dr. William Boyd Reading, F.A.C.P., of Galveston, Texas, died on February 2, 1950. He was born in Galveston in 1890 and received his medical degree from the University of Texas School of Medicine in 1914. Early in his career he became interested in pediatrics and did postgraduate work in this field at the Babies Hospital in New York City, at the St. Louis Children's Hospital and at the Harvard Medical School.

Dr. Reading became Professor of Pediatrics at the University of Texas School of Medicine in 1923, and served in this capacity until the time of his death. He was President of the Texas Pediatric Society in 1933, state chairman of the American Academy of Pediatrics in 1938, and was a diplomate of the American Board of Pediatrics. He was a member of the Texas State Medical Association, Southern Medical Association, and a Fellow of the American Medical Association. He was elected a Fellow of the American College of Physicians in 1929. During World War I, he served in the Medical Corps of the United States Army with service in the British Army from 1917 to 1919. Dr. Reading was an affable gentleman, a competent pediatrician and was greatly beloved by his colleagues.

D. W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

DR. FRANK WILLIAM SPICER

Frank William Spicer, A.B., M.D., F.A.C.P., was born in Blairstown, Iowa, November 30, 1878, and died in Duluth, Minn., on January 21, 1950. He was graduated from the University of Pennsylvania School of Medicine in 1908, and served a year's internship at the Methodist Hospital in Philadelphia. After practicing medicine for a period in Crystal Falls, Mich., he moved to Duluth, Minn., in 1912. Except for his service in the United States Army Medical Corps, which included overseas duty, he spent the rest of his active career in Duluth.

Dr. Spicer received his preliminary education in Iowa, was graduated from Coe College in 1899, and gave several years to teaching. First he taught Greek and History in the high school in Northfield, Minn. In 1903 he accepted a teaching assignment in the Philippines during a period after the Spanish-American War when, under American guidance, a notable plan of advanced education was inaugurated. In later life he frequently referred to his experience in the Philippines, and without question it greatly helped to broaden the life already capable of encompassing the best of our American traditions, scholastic, social, moral and intellectual. Frank's father was a doctor, and it was this fact and his experience in the Philippines, and his visits to China, Japan and Guam, that developed his interest and the urge to return to the states and study medicine.

Frank Spicer was one of the earliest physicians in Northeastern Minnesota to devote all his time to Internal Medicine. He cemented interest in his field by obtaining membership in the American College of Physicians in 1922, by association with the Minnesota Society of Internal Medicine, and through his years of activity in establishing the medical staffs of both St. Mary's and St. Luke's Hospitals in Duluth. At one time he served as chief of medical service in each of these hospitals, and did much to guide his fellows wisely and conservatively. He was also active in the work of the American Legion and had much to do with conservative direction of his fellow members.

In 1939 he published "Trauma and Internal Disease" (J. B. Lippincott Company). To the writing of this work he gave several years of research and review of the extensive literature. The book has found a favorable reception among critics and a place in many private and public medical libraries.

Dr. Spicer was a member of the First Presbyterian Church in Duluth, where he met and married Madeline Miller, the church organist, in 1915. To them were born four children: Dr. Frank W. Spicer, Jr., Buffalo, N. Y.; Richard G. Spicer, Duluth, Minn.; Mrs. Thomas G. Bell, Jr., Duluth, Minn.; and Mrs. Clark MacGregor, Wayzata, Minn. In addition, three grandsons and two granddaughters survive him.

Frank W. Spicer was an earnest, conscientious student and citizen all his life. In his later years he used to be commended for his very particular and specific guidance of an appreciative clientele, teaching them the while "to grow gracefully." In him they found the best of examples and the most wholesome of guidance.

E. L. TUOHY, M.D., F.A.C.P.

DR. JOHN FRANCIS KENNEY

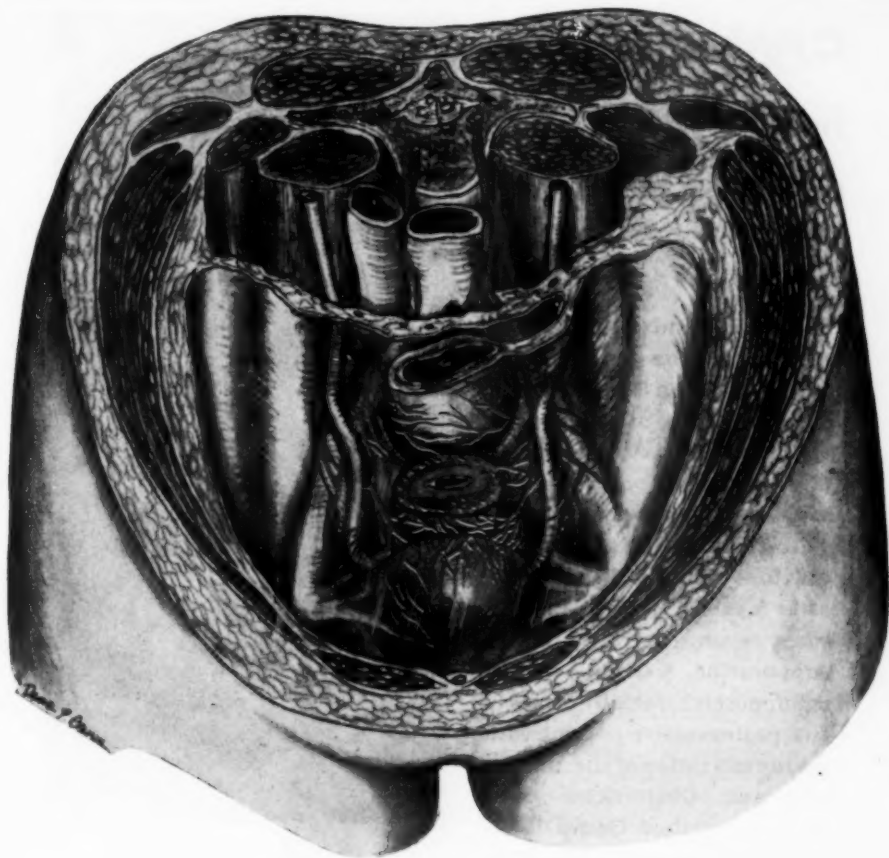
Dr. John Francis Kenney, Pawtucket, R. I., a Fellow of the American College of Physicians since 1933, died on March 20, 1950. He was born in New Bedford, Mass., January 15, 1890, and graduated from Tufts College Medical School in 1913, receiving the degree of M.D., cum laude.

He had internships at the Boston Floating Hospital and the Rhode Island Hospital in Providence. He did postgraduate work at Medical Centers in the United States and Europe. He practiced internal medicine in Pawtucket for thirty years, and was very active in the work of the Memorial Hospital in Pawtucket, where he was, for a number of years, Director of Laboratory and Chief of the Medical Staff. He retired from active practice about five years ago, but had continued as consultant at the Memorial Hospital and other hospitals in Providence and in the State of Rhode Island. He was President of the Rhode Island Medical Society in 1945-1946. He served as President of the Pawtucket Medical Society and was a former President of the Industrial Physicians and Surgeons of New England. He was a diplomate of the American Board of Internal Medicine. He was a Life Member of the American College of Physicians, a Fellow of the American Medical Association, Fellow of the American Association of Industrial Physicians, member of the American Gastroenterological Association, member of the Rhode Island Medical Society, and a member of the Rhode Island Pathological Society and of the Rhode Island Industrial Physicians. He was a member of the Board of Examiners in the Basic Sciences of the State of Rhode Island, and a member of the Advisory Board of the Rhode Island Curative Center. While he was Chief of the Medical Staff at the Pawtucket Memorial Hospital he inaugurated an annual all-day clinic session, at which outstanding leaders in medicine and surgery in the United States present papers and conduct clinics. This activity has become an annual event at the Memorial Hospital and has been named in honor of Dr. Kenney as, "John F. Kenney Annual Clinic of the Memorial Interns' Alumni Association."

Dr. Kenney was an outstanding leader in medicine in the State of Rhode Island. He was highly regarded and respected by his colleagues, patients, and the general public.

HERMAN A. LAWSON, M.D., F.A.C.P.,

Governor for Rhode Island



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Literature and Samples on Request

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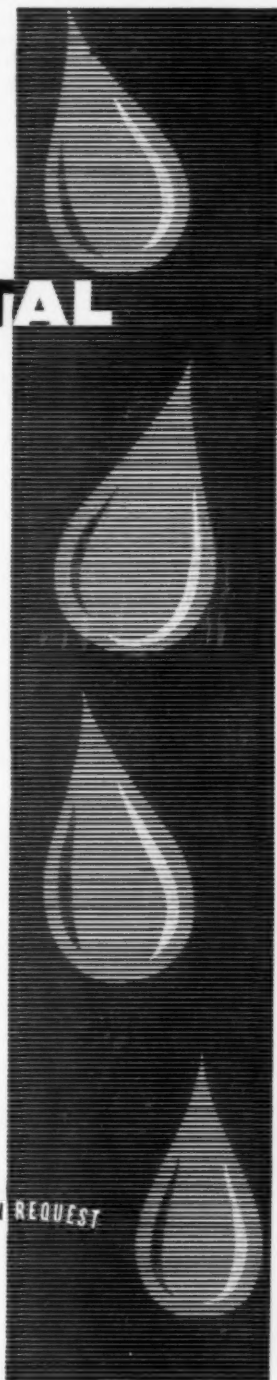
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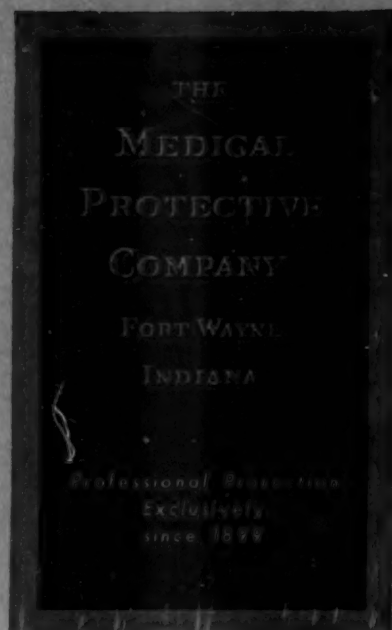
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June, 1950

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Blakiston Company, The.....	3	A. J. Parker Company.....	49
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Buffington's Inc.....	30	Sanborn Company.....	40
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S. H. Camp and Company.....	44	G. D. Searle & Co.....	22, 23, 43
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Chilcott Laboratories.....	7	Smith, Kline & French Laboratories.....	25
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Commercial Solvents Corporation.....	32	U. S. Vitamin Corporation.....	12
Davies, Rose & Company, Limited.....	38	Varick Pharmacal Co., Inc.....	24
Denver Chemical Mfg. Co., Inc., The.....	47	Wander Company, The.....	11
Devereux Schools.....	6	Williams & Wilkins Company, The.....	2
C. B. Fleet Co., Inc.....	34	Winthrop-Stearns, Inc.....	31
Flint, Eaton & Company.....	39	Woodward Medical Personnel Bureau.....	46
General Electric X-Ray Corporation.....	29	Wyeth Incorporated.....	33
Hille Laboratories.....	20		

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